Exhibit 100

(4)

Draft Screening Assessment

Talc
($Mg_3H_2(SiO_3)_4$)

Chemical Abstracts Service Registry Number
14807-96-6

Environment and Climate Change Canada
Health Canada

December 2018

Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc. The Chemical Abstracts Service Registry Number (CAS RN[1]) for talc is 14807-96-6. This substance is among those substances identified as priorities for assessment as it met categorization criteria under subsection 73(1) of CEPA.

Talc is a naturally occurring mineral. According to information reported under section 71 of CEPA and publically available information, in 2011 talc was manufactured in Canada in quantities ranging between 50 to 75 million kg, and in 2016, approximately 100 million kg of talc was imported. In Canada talc is used in adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials; ceramics; electrical and electronics; textiles; floor coverings; ink, toner, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products, mixtures, and manufactured items; plastic and rubber materials; toys, playground, and sporting equipment; and in water treatment. The major uses in Canada align with major global uses of talc. Talc is an ingredient in self-care products and is a permitted food additive. In North America, approximately 3 to 4 % of the talc produced and sold is used in cosmetics. High-purity talc is used in cosmetics, while lower-grade talc is used in commercial applications.

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) approach. The ERC-I is a risk-based approach that employs multiple metrics, considering both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of new PNEC values when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environment concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment. The ERC-I identified talc as having a low potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is a low risk of harm to the environment from talc. It is proposed to conclude that talc does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or

---

[1] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Talc has been reviewed internationally by other organizations, including the International Agency for Research on Cancer (IARC) and the Danish Environmental Protection Agency. These assessments informed the human health risk assessment.

No critical health effects were identified via the oral or dermal routes of exposure. As such, oral exposure to talc resulting from food intake and self-care products is not of concern. Inhalation exposure from industrial and commercial uses of talc was not identified to be of concern for human health given the limited number of sites producing and processing talc in Canada. Rather, the focus of the assessment is on inhalation and perineal exposure to certain self-care products containing cosmetic- or pharmaceutical-grade talc.

With respect to inhalation exposure, non-cancer lung effects were identified as a critical health effect for risk characterization on the basis of United States National Toxicology Program studies conducted with rats and mice exposed to cosmetic-grade talc. There is potential for inhalation exposure to talc powder during the use of certain self-care products (e.g., cosmetics, natural health products, non-prescription drugs formulated as loose powders). Self-care products formulated as pressed powders (e.g., face makeup) are not of concern. Margins of exposure between air concentrations following the use of dry hair shampoo and critical lung effects observed in animal studies are considered adequate to address uncertainties in the health effects and exposure databases. Margins of exposure between air concentrations following the use of loose powders (e.g., body powder, baby powder, face powder, foot powder) and critical lung effect levels observed in animal studies are considered potentially inadequate to address uncertainties in the health effects and exposure databases.

The meta-analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. Further, available data are indicative of a causal effect. Given that there is potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs), a potential concern for human health has been identified.

Based on the available information, it is proposed that there is potential for harm to human health in Canada at current levels of exposure. Therefore, on the basis of the information presented in this draft screening assessment, it is proposed to conclude that talc meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that talc meets one of the criteria set out in section 64 of CEPA.

Talc is proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

Table of Contents

List of Tables

1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc to determine whether this substance presents or may present a risk to the environment or to human health. This substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) approach (ECCC 2018). The ERC-I is a risk-based approach that employs multiple metrics, considering both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of a new PNEC value when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment.

With respect to human health, this draft screening assessment includes the consideration of information on chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. Relevant data were identified up to August 2018. Empirical data from key studies, as well as results from models, were used to reach proposed conclusions. Talc has been reviewed internationally through the International Agency for Research on Cancer (IARC) Monographs Programme, United States Environmental Protection Agency (U.S. EPA), the Joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the Danish Environmental Protection Agency (Danish EPA). Talc was also assessed by the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) in Germany and the Cosmetic Ingredient Review (CIR) Expert Panel. These evaluations and reviews were used to inform the health effects characterization in this screening assessment. This assessment focuses on health effects associated with cosmetic-grade talc and not on potential impurities, such as asbestos. Engineered nanomaterials composed of or containing talc are not explicitly considered in this assessment.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and the Consumer Product Safety Directorate at Health Canada and incorporates input from other programs within these departments. The ecological portion of the assessment is based on the ERC-I document (published May 11, 2018), which was subject to an external peer review and a 60-day public comment period. The human health portion of

this assessment has undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Ms. Lopez, Ms. Super, and Ms. Jeney of Tetra Tech. Although external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[2] This draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substance

Talc (CAS RN[3] 14807-96-6) is one of the softest naturally occurring minerals, made up of magnesium, silicon, and oxygen (ChemIDplus 1993-). The term talc refers to both the pure mineral and a wide variety of soft, talc-containing rocks that are mined and used for a variety of applications (Kogel et al. 2006). Relatively pure talc ore is also referred to as steatite, and soapstone refers to impure, massive talc rock (Fiume et al. 2015).

The mineral talc is composed of triple-sheet crystalline units, consisting of two silicate sheets composed of SiO_4 tetrahedra joined by edge-link $MgO_4(OH)_2$ (Zazenski et al. 1995). These layers, held together loosely via van der Waals forces, slide over one another easily, giving talc its slippery feel and accounting for its softness (Fiume et al. 2015). The size of an individual talc platelet (i.e., a few thousand elementary sheets) can vary from approximately 1 µm to over 100 µm, depending on the conditions of formation of the deposit (Eurotalc 2017). The individual platelet size determines the lamellarity of a sample of talc. Highly lamellar talc will have large individual platelets, whereas microcrystalline talc will have small platelets. Other inorganics in place of magnesium and silicon are common in talc; for example, aluminum and iron may substitute for silicon in the tetrahedral sites, or manganese may substitute for magnesium in the octahedral positions (Zazenski et al. 1995).

---

[2] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion on the basis of the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

[3] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

Commercially exploited talc contains 20 to 99 % of the pure mineral (Kogel et al. 2006). Some of the most common minerals that occur with talc are carbonates (e.g., dolomite, calcite, magnesite) and chlorite (i.e., magnesium aluminum silicate) (CIR 2013). Less common minerals include quartz, mica, iron oxides, pyrite, serpentine, and amphibole. Selective mining, ore processing, and beneficiation can remove many of the impurities (Kogel et al. 2006). There is a trend towards upgrading and higher-purity talc; however, many applications require the properties of the minerals associated with talc (Kogel et al. 2006). The purity of the source talc will influence its uses.

There are different grades of talc that refer to the purity (presence of other minerals). Pharmaceutical-grade talc conforms to the United States Pharmacopeia (USP) specifications (or similar specifications); these specifications require the absence of asbestos and set limits on iron, lead, calcium, and aluminum (USP 2011). As per B.01.045 of the *Food and Drug Regulations*, when used as a food additive talc must comply with Food Chemical Codex specifications or the Combined Compendium of Food Additive Specifications, prepared by the Joint FAO/WHO Expert Committee on Food Additives, and must be free from asbestos (FAO 2006).

Cosmetic-grade talc should comply with USP standards that require a limit of 20 ppm lead and an absence of asbestos (Fiume et al. 2015). Historically, some talc source materials were contaminated with asbestos; however, in 1976 the Cosmetic Toiletry Fragrance Association (CTFA) set purity standards for cosmetic-grade talc (Fiume et al. 2015). In Canada, the *Prohibition of Asbestos and Products Containing Asbestos Regulations* to be made under CEPA 1999 will prohibit asbestos above trace levels in consumer products, including cosmetics. Health effect studies on cosmetic-grade talc cited in this assessment were considered to be free of asbestos.

Talc is milled to different particle sizes for specific commercial applications. Most talc for cosmetics and pharmaceuticals are pure 200-mesh roller-milled talc (Kogel et al. 2006). In 200-mesh talc (preferred for body powder and deodorants), the particle size distribution allows 95 to 99 % of the product to pass through a 200-mesh (74 µm) screen (Zazenski et al. 1995; Kogel et al. 2006). The finer 325-mesh talc is also used in cosmetic-, pharmaceutical-, and food-grade formulations, where 95 to 99 % of the product passes through a 325-mesh (44 µm) screen.

3. Physical and chemical properties

A summary of physical and chemical properties of talc is presented in

Table 3-1. Talc is hydrophobic and lipophilic (Kogel et al. 2006).

Table 3-1. Experimental physical and chemical property values (at standard temperature) for talc

Property	Range	Key reference
Physical state	solid, powder	HSDB 2005
Melting point (°C)	1500	Eurotalc 2017
Vapour pressure (mm Hg)	approx. 0, negligible at 20°C	OSHA 1999; NIOSH 2014
Water solubility (mg/L)	insoluble	HSDB 2005
Specific gravity (unitless)	2.58–3.83	HSDB 2005

4. Sources and Uses

Talc is a naturally occurring mineral, and there are deposits of talc in most provinces of Canada (Kogel et al. 2006). Currently, there is one producing mine (open-pit) and concentrator facility in Canada, in Penhorwood Township near Timmins, Ontario, and one micronizing facility in Timmins (Kogel et al. 2006; MAC 2016; NPRI 2018). The talc ore from the mine is approximately 45 % pure, with magnesite, magnetite, chlorite, and serpentine as the major impurities (Kogel et al. 2006). After beneficiation, this mine and micronizing facility produces talc primarily for the paper, plastics, paint, and ceramic sectors (Kogel et al. 2006). In 2017, China was the largest producer of talc, followed by India, Brazil, Mexico, and Korea (USGS 2018). The major uses of talc globally include paper, plastics, paint, ceramics, putties, and cosmetics (USGS 2000; Kogel et al. 2006; EuroTalc 2017; USGS 2018) and are aligned with Canadian uses.

On the basis of information submitted pursuant to a CEPA section 71 survey for the year 2011, talc was reported to be manufactured and imported in Canada at quantities ranging from 50 to 75 million kg (EC 2013).[4] According to the Canadian International Merchandise Trade (CIMT) database, in 2016, 99 549 000 kg of natural steatite and talc, crushed or powdered (Harmonized System, HS code 252620) and 4 656 000 kg of natural steatite and talc, not crushed, not powdered (HS code 252610) were imported into Canada (CIMT 2017).

According to information reported pursuant to a CEPA section 71 survey, results from voluntary stakeholder engagement (ECCC, HC 2017), and a search of websites from talc producers, manufactured or imported talc is used in Canada in: adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials (e.g., wood and engineered wood); ceramics; electrical and electronics; textiles; floor coverings; ink, toner, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products,

[4] Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (EC 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

mixtures, or manufactured items; plastic and rubber materials; toys, playground, and sporting equipment; and in water treatment.

Talc is a formulant in pest control products registered in Canada (Health Canada 2010, Personal communication, email from the Pest Management Regulatory Agency, Health Canada to the Risk Management Bureau, Health Canada, dated March 29, 2017; unreferenced).

Additionally, in Canada talc is on the List of Permitted Food Additives with Other Accepted Uses for limited uses in a small number of foods (Health Canada [modified 2017]). Talc can be used as a coating agent on dried legumes and rice and as a filler and dusting powder for chewing gum as per the List of Permitted Food Additives with Other Accepted Uses, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. It may be present in food packaging materials and in incidental additives[5] used in food processing establishments (email from the Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated March 31, 2017; unreferenced).

Talc is present in approximately 8500 self-care products.[6] Talc is marketed or approved as a non-medicinal ingredient in approximately 1600 human and veterinary drug products in Canada, including approximately 150 over-the-counter (OTC) or non-prescription products (email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017; unreferenced). Talc is listed in the Natural Health Products Ingredients Database (NHPID [modified 2018]) with a medicinal role and classified as a natural health product (NHP) substance falling under item 7 (a mineral) of Schedule 1 to the *Natural Health Products Regulations* and with a non-medicinal role (NHPID [modified 2018]). Talc is listed in the Licensed Natural Health Products Database (LNHPD) as being present as a medicinal or non-medicinal ingredient, in currently licensed natural health products in Canada (LNHPD [modified 2018]). Talc is present as a medicinal or a non-medicinal ingredient in approximately 2000 active licensed NHPs. Talc is listed as a medicinal ingredient in diaper rash products in concentrations ranging from 45 to 100 % in the Diaper Rash Monograph (Heath Canada 2007); however, there are no diaper rash products listed in the LNHPD containing talc as a medicinal ingredient (LNHPD [modified 2018]). Talc is permitted as a medicinal ingredient in the monograph for Traditional Chinese Medicine Ingredients (Health Canada 2015).

---

[5] While not defined under the Food and Drugs Act (FDA), incidental additives may be regarded, for administrative purposes, as those substances that are used in food processing plants and that may potentially become adventitious residues in foods (e.g., cleaners, sanitizers).

[6] Self-care products are products available for purchase without a prescription from a doctor, and fall into one of three broad categories: cosmetics, natural health products, and non-prescription drugs.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, talc is an ingredient in approximately 6500 cosmetic products in Canada (dated April 5, 2017, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Talc is considered a restricted ingredient in cosmetics.[7] The Cosmetic Ingredient Hotlist entry for cosmetics containing talc in powder form intended to be used on infants and children indicates that product labels should display text to the effect of "keep out of the reach of children" and "keep powder away from child's face to avoid inhalation that can cause breathing problems." High-purity talc (fewer impurities of other minerals) is used in cosmetics, while lower-grade talc is used in the many commercial applications mentioned above. In North America, approximately 3 to 4 % of the talc produced and sold is used in cosmetics (Kogel et al. 2006; USGS 2018).

Condoms and medical gloves are regulated as Class II medical devices in Canada under the *Medical Devices Regulations* and may be sources of exposure if talc is present as a dry lubricant. However, a 1998 study did not find talc in a small survey of condoms tested in Canada (Douglas et al. 1998). Condom standards require dry lubricants to be bioabsorbable, such as starch and calcium carbonate (WHO, UNFPA, FHI 2013). Starch is more commonly used as dry powder lubricant on condoms (Douglas et al. 1998). There was also a shift from the use of talc as a dry lubricant on medical patient examination gloves to cornstarch in the 1980s (Lundberg et al. 1997). In 2016, the U.S. Food and Drug Administration banned powdered patient examination gloves (United States 2016).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I). The ERC-I is a risk-based approach that employs multiple metrics that consider both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past domestic and international assessment PNECs and water quality guidelines. When no suitable existing PNEC or water quality guideline was found, hazard endpoint data were collected and, dependent on data availability, either a species sensitivity distribution (SSD) or an assessment factor (AF) approach was taken to derive a new PNEC value. In the case of talc, hazard endpoint data from the Organisation for Economic Co-operation and Development

[7] Talc is described as a restricted ingredient on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA), or may contravene one or more provisions of the *Cosmetic Regulations*. Section 16 of the FDA states that "no person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user." In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada [modified 2018]).

Screening Information Dataset (SIDS) for synthetic amorphous silicates (OECD 2004) were identified for read across (ECCC, HC 2017) and an AF approach was used to derive a PNEC value of 40 mg/L.

Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. The generic near-field exposure model used input data, when available, from the National Pollutant Release Inventory (NPRI), the DSL–Inventory Update (DSL-IU), international trade data from the Canada Border Services Agency (CBSA), and third-party market research reports to generate PECs. In the case of talc, input data from the DSL-IU and CBSA were available.

Modelled PECs were compared to PNECs, and statistical metrics considering both the frequency and magnitude of exceedances were computed and compared to decision criteria to classify the potential for ecological risk as presented in ECCC (2018). The results are summarized in Table 5-1. The ERC-I identified talc as being of low ecological concern.

Table 5-1. Ecological risk classification of inorganics results for talc

Monitoring (total/extractable)	Monitoring (dissolved)	Modelling (DSL-IU)	Modelling (NPRI)	Modelling (CBSA)	Overall ERC-I score
NA	NA	Low	NA	Low	Low

Abbreviations: NA, Not Available.

6. Potential to cause harm to human health

6.1 Health effects assessment

Talc was previously reviewed internationally by the IARC, and an IARC monograph is available (IARC 2010). Additionally, talc was reviewed by the United States Environmental Protection Agency (U.S. EPA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) in Germany, and the Danish Environmental Protection Agency (Danish EPA) (U.S. EPA 1992; JECFA 2006; MAK-Commission 2012; Danish EPA 2016). Talc's safety in cosmetic uses was also assessed by the CIR Expert Panel (CIR 2013; Fiume et al. 2015).

A literature search was conducted from the year prior to the most recent assessment (the 2016 Danish EPA review), i.e., from January 2015 to January 2018. No health effects studies that could impact the non-cancer risk characterization (i.e., result in different critical endpoints or lower points of departure than those stated in existing reviews and assessments) for oral, dermal, or inhalation exposures were identified. For perineal exposures, recently published literature was identified and considered in the assessment.

The health effects of talc are outlined by route of exposure in the following sections.

Toxicokinetics

Talc is poorly absorbed via the oral route of exposure. Following gavage administration of radiolabelled talc to rodents, the majority of the administered dose (AD) remained in the gastrointestinal (GI) tract and was eliminated and recovered in the faeces (≥ 95.8 % of AD) within three to four days of dosing (Wehner et al. 1977a; Phillips et al. 1978). Less than 2 % of the AD was recovered in the urine; however, this was mainly attributed to contamination from faeces during collection, with true absorption and urinary clearance expected to be even lower. At 24 hours post administration, less than 2 % of the AD remained in the carcass of hamsters; no radioactivity was detected in mouse carcasses at this time point. In rats and guinea pigs, only trace amounts of radioactivity remained in the GI tract at 10 days post administration.

As an insoluble solid, talc is not expected to be absorbed when applied to healthy and intact skin. There are no indications of dermal absorption following talc exposure (MAK-Commission 2012).

Inhalable talc particles (<10 µm) are eliminated from the respiratory tract via mucociliary clearance. In female Syrian hamsters that were administered aerosolized neutron-activated cosmetic talc at concentrations of 40 to 75 mg/m^3 (95% pure; MMAD 6.4 to 6.9 µm) over a 2-hour exposure period, 6 to 8 % of the AD was deposited into the alveoli (Wehner et al. 1977b). The biological half-life following a single exposure was estimated to be between 7 and 10 days, with complete alveolar clearance after 4 months. There was no translocation of talc from the respiratory tract to the liver, kidneys, ovaries, or other parts of the body. Lung clearance was noted to be longer in other species. The Danish EPA (2016) noted that talc, including the respirable fraction (< 4 µm), is not absorbed following inhalation, but is retained in the lung tissue. They further stated that lung burdens were proportional to respired concentrations, and clearance became impaired with increasing exposures. Pulmonary retention half-lives for talc particles in the lungs of rats from a chronic inhalation study were estimated to be as long as 300 days (Oberdorster 1995). Other authors (Pickrell 1989; MAK-Commission 2012) noted similar findings indicating that with repeat exposures, alveolar clearance in rats may be impaired at concentrations of only 2 mg talc/m^3 air.

Talc particles have been observed and detected in the ovaries of humans (Heller et al. 1996a, 1996b), and perineal exposure to talc has also been associated with a presence of talc in lymph nodes and ovaries of women diagnosed with ovarian cancer (Heller et al. 1996b; Cramer et al. 2007). Migration of talc particles from the vagina to the ovaries has been identified as a plausible explanation of these findings (Henderson et al., 1986), and retrograde movement of talc particles in humans through the reproductive tract to the ovaries has been suggested (Heller et al. 1996b; Cramer et al. 2007). Inert particles with the same size as talc (5 to 40 µm in diameter) and placed in the vagina can be transported to the upper genital tract (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979).

According to a review by the MAK-Commission (2012), there are no indications of metabolism via typical degradation pathways from which toxicologically relevant degradation products may develop.

Health Effects

Oral route of exposure

Talc was considered be of low concern with respect to human health via oral exposure. Repeated-dose testing with talc in animals did not produce any adverse effects via oral exposure with respect to repeated-dose toxicity, carcinogenicity, reproductive/developmental toxicity, or mutagenicity (Gibel et al. 1976; Wagner et al. 1977; NTP 1993; IARC 2010; Danish EPA 2016).

Talc has not been shown to produce adverse effects when ingested orally; as a result, the use of talc in various tablet formulations was not considered hazardous via the ingestion route (Hollinger 1990; U.S. EPA 1992).

In addition, the Commission of the European Communities' report on Dietary Food Additive Intake in the European Union identified talc as having an Acceptable Daily Intake (ADI) of "not-specified." The JECFA has also assessed talc and assigned an ADI as "not specified" due to the lack of toxicity from oral exposure. The substance was considered not to be a hazard to human health at oral intake levels noted in total diet surveys, which represent the majority of the sources of oral exposure for this substance (IARC 1987; EU [modified 2001]). Furthermore, talc is considered as "generally recognized as safe" when used as a food additive in the United States (U.S. FDA GRAS list) without being subject to pre-market approval requirements (U.S. FDA 2015; 2016).

Dermal route of exposure

There are limited data available on repeated-dose studies via dermal exposure to talc (Danish EPA 2016). In the available literature, only one repeated-dose dermal toxicity study was identified (Wadaan 2009). Severe limitations were noted for this study, including a lack of information on the test substance and the dose applied, as well as a lack of detail regarding the test animals. Skin dryness and erosion were noted; however, application sites were shaved, indicating that talc may have been applied to broken skin. As such, the results of this study were not considered appropriate to inform the characterization of health effects via dermal exposure. Additionally, there were no indications of irritation, sensitization, or dermal absorption following exposure to unabraded and/or non-diseased skin (MAK-Commission 2012). A three-day occlusive application of pharmaceutical-grade talc did not show any signs of irritation in 5 human volunteers (Frosch and Kligman 1976, as reported in MAK-Commission 2012).

Case reports, however, do indicate that the application of talc to diseased or broken skin can cause the formation of granulomas, particularly if the talc particles have a large diameter (MAK-Commission 2012; CIR 2013; Fiume et al. 2015). Granulomas have

been observed in the umbilical regions of infants, in the testes, on the vocal cords, in the urinary tract, and during phlebectomies following contact with talc-powdered surgical gloves (Ramlet 1991, Simsek et al. 1992, as reported in MAK-Commission 2012). As a result, the CIR concluded that "talc should not be used on skin where the epidermal barrier is removed or on skin that has greater than first degree burns."

Although dermal contact with talc is expected from the use of various products available to consumers, talc is a solid powder that is insoluble in water (Table 3-1). As a result, it cannot readily penetrate intact skin, and therefore systemic absorption through the skin is not expected. Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), a dermal health effects endpoint has not been identified for talc.

Inhalation route of exposure

Human studies

The Danish EPA (2016) noted that talc is not absorbed via inhalation. Rather, particles are retained in the lung, and lung burdens increase proportionally with exposure concentrations or frequency. The report detailed epidemiological data that noted mortalities in workers due to lung diseases, following exposures to talc. However, it was stated that there was no increase in the lung cancer rate in talc millers in the absence of exposure to carcinogens. A recent meta-analysis by Chang and colleagues (2017) reported a positive association with lung cancer in workers exposed to talc; however, co-exposure to other hazardous materials in the workplace and smoking were not adequately accounted for.

The chronic inhalation of talc leads to lung function disorders and fibrotic changes in humans. Since talc particles are persistent, particles accumulate in human lung tissue. This accumulation may lead to both an impairment of the self-purification function (reduced ability to fight infections) and inflammatory changes and fibrosis. Talc particles may be enclosed in a foreign-body granuloma as the result of an inflammatory reaction. The immobility of the macrophages, which is restricted by the phagocytized talc particles, leads to changes in the function of these cells and subsequently to chronic inflammatory reactions (Gibbs et al. 1992).

In humans, there are reports of pure talc-induced pneumoconiosis or talcosis following inhalation exposure to talc. Talcosis has been reported to occur in miners, millers, rubber workers, and other occupational groups exposed to talc without asbestos or silica (Vallyathan and Craighead 1981; Feigin 1986; Gibbs et al. 1992; Akira et al. 2007). Specifically, a recent longitudinal survey of French and Austrian talc workers found that the prevalence of small radiological opacities and decreases in lung function parameters were related to cumulative exposure. The mean estimated talc dust concentration during the mean duration of follow-up (14.5 years) was 1.46 mg/m^3 (Wild et al. 2008). Case reports indicate that patients present with non-specific complaints, including progressive exertional dyspnea, dry or productive cough, with indications of

lung lesions (Marchiori et al. 2010; Frank and Jorge 2011). Talcosis has been shown to occur in children and adults, with symptoms that developed shortly after acute to short-term exposure or up to 10 years later (Patarino et al. 2010; Shakoor et al. 2011). Inhalation of talc has been known to cause pulmonary effects, even following single acute exposures, as reported in a 10-year-old child who had a history of a single exposure to talc at two years of age (Cruthirds et al. 1977). Another case report detailed a seven-year-old child who developed asthma and reduced lung function after a single exposure event (Gould and Barnardo, 1972). Additionally, a 52-year-old woman who used baby talcum powder regularly at least twice a day (usually after bathing for personal hygiene and habitually applying it to her bed sheets nightly) for 20 years was reported to have dyspnea, along with a persistent dry cough and unintentional rapid weight loss. A radiographic exam noted evidence of interstitial lung disease with fibrosis (Frank and Jorge 2011).

Other relevant case reports include the case of a 55-year-old woman, occupationally exposed to talc as a dusting agent on packed rubber balls from 1958 to 1968, who was reported to develop dyspnea during the first five years after exposure (Tukiainen et al. 1984); and a 62-year-old woman occupationally exposed to talc for five years who was reported to have progressive lung fibrosis for more than 40 years (Gysbrechts et al. 1998).

Animal studies

In a repeated-exposure study conducted by the U.S. National Toxicology Program (NTP), groups of F334/N rats were exposed to aerosolized talc via the inhalation route of exposure. Test animals were exposed for 6 hours per day, 5 days per week, for up to 113 weeks (males) or up to 122 weeks (females) to aerosols of 0, 6, or 18 mg/m^3 talc (49 or 50 males per group, 50 females per group) (NTP 1993). Mean body weights of rats exposed to 18 mg/m^3 talc were slightly lower than those of controls after week 65. No clinical observations were attributed to talc exposure. Absolute and relative lung weights of male and female rats exposed to 18 mg/m^3 talc were significantly greater than those of controls. Inhalation exposure produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs. Granulatomous inflammation, which was evident as early as 6 months (first histopathological examination), occurred in nearly all exposed rats, and the severity increased with exposure duration and concentration. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near the foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In exposed male and female rats, there was a concentration-related impairment of respiratory function, beginning at 11 months, which increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume (total lung capacity, vital capacity, and forced vital capacity), lung compliance, gas exchange efficiency (carbon monoxide diffusing capacity), and non-uniform intrapulmonary gas distribution (NTP 1993).

In female rats at 18 mg/m^3 talc, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) were significantly greater than those of controls (NTP 1993). The incidences of lung neoplasms in exposed male rats were similar to those in controls. Adrenal medulla pheochromocytomas (benign, malignant, or complex [combined]) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 talc groups were significantly greater than those of controls (NTP 1993).

The NTP (1993) concluded that there was some evidence of carcinogenic activity of talc in male rats on the basis of an increased incidence of benign or malignant pheochromocytomas of the adrenal gland. The NTP also concluded that there was clear evidence of carcinogenic activity of talc in female rats on the basis of increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

In a subsequent symposium, experts from the NTP, along with academic, industry, and government experts re-examined the results of the chronic inhalation studies. The general consensus from the expert panel was that the highest dose tested (18 mg/m^3) exceeded the Maximum Tolerated Dose (MTD) and as such, the neoplasms noted were not relevant to human health risk assessment (Carr 1995). A similar conclusion was rendered by Warheit et al. (2016). In addition, the Danish EPA (2016) and the MAK-Commission attributed lung tumours in female rats to the general particle effect of granular biopersistent dusts, which manifests as tumours in rodents only, and not the specific effect of the talc particles. They also attributed the pheochromocytomas to an increase in cell proliferation due to hypoxia, which was considered to be a high-dose effect (MAK-Commission, 2012).

A chronic, repeated-exposure study was conducted in B6C3F1 mice via the inhalation route of exposure (NTP 1993). Test animals were exposed for 6 hours per day, 5 days per week, for up to 104 weeks to aerosols of 0, 6, or 18 mg/m^3 talc (47 to 49 males per group, 48 to 50 females per group). Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. There were no clinical findings attributed to talc exposure. Inhalation exposure of mice to talc at both concentrations was associated with chronic active inflammation and the accumulation of macrophages, which contained talc, in the lung. In contrast to rats, hyperplasia of the alveolar epithelium, squamous metaplasia, or interstitial fibrosis were not associated with the inflammatory response in mice, and the incidences of lung neoplasms in exposed and control groups of mice were similar. Accumulations of macrophages (histiocytes) containing talc particles were also present in the bronchial lymph node. The critical-effect level and corresponding health effects endpoint was a lowest observed adverse effect concentration (LOAEC) of 6 mg/m^3 for non-cancer lung effects (NTP 1993).

Doses used in the NTP chronic studies were selected on the basis of the results of a 4-week inhalation study (1993) in which rats and mice were exposed to talc at 0, 2, 6, or 18 mg/m^3, 6 hours a day, 5 days a week. Lung burdens were noted to be increased in a

dose-dependent manner, with overload noted by the study authors at 6 and 18 mg/m^3 in rats but not at any dose in mice. In both species (mice and rats), a minor macrophage infiltration of lung tissue was the only health effect noted in the high-dose animals, while animals in the mid- and low-dose groups were without treatment-related effects.

In a review of the NTP studies, Oberdorster (1995) revisited the lung deposition data and particle accumulation kinetics in the lungs of rats and mice in those studies, demonstrating that impaired clearance and lung overload was reached at 6 mg/m^3 and above, for both sexes, in rats and mice.

A no-observed adverse effect concentration (NOAEC) of 2 mg/m^3 was derived from the 4-week study, on the basis of increased lung burden and impaired clearance at a LOAEC of 6 mg/m^3 following 4-weeks of dosing, which led to non-cancer lung lesions at this concentration when the duration of dosing was extended. Granulatomous inflammation and alveolar epithelial hyperplasia were noted at a 6 month interim sacrifice in the chronic rat inhalation study, with interstitial fibrosis and impaired lung function noted in some animals at 11 months. As noted previously, following a single exposure in rats, the biological half-life for ciliary clearance was between 7 and 10 days, indicating that previous exposure would not have cleared prior to subsequent exposures, leading to a build-up in lung tissue. A re-examination of the NTP lung burden data by Oberdorster (1995) estimated that lung retention half-lives of talc particles were between 250 and 300 days in the rat chronic study. On the basis of this information, it was considered relevant to combine the NTP studies for the derivation of an appropriate point of departure for lung effects associated with repeated inhalation exposures.

The Danish EPA (2016) used the LOAEC of 6 mg/m^3 from the chronic NTP studies (mice and rats) and a NOAEC of 1.5 mg/m^3 for talc-induced non-cancer lung effects in the longitudinal survey of French and Austrian talc workers (Wild et al. 2008) to establish a health-based quality criterion for ambient air (QC_{air}) of 0.004 mg/m^3.[8]

While human occupational studies and case studies are available, these studies do not provide accurate measures of exposure for use in risk characterization. However, human studies do note a similar range of lung effects and disease as animal models. As such, results from the animal studies noted above were selected for the non-cancer risk characterization. On the basis of the NTP studies with rats and mice exposed to cosmetic-grade talc, a NOAEC of 2 mg/m^3 for non-cancer lung effects is considered to be appropriate for the inhalation route of exposure for short- or long-term use (given the long half-life and slow lung clearance of talc from the lungs, even episodic exposures would be expected to increase lung load). The NOAEC of 2 mg/m^3 was adjusted according to U.S. EPA guidance on inhalation risk assessment for a comparison with

[8] The health-based quality criterion in ambient air (QC_{air}) is a reference concentration that refers to the maximum permissible contribution to air from industrial sources.

exposure estimates (U.S. EPA 1994, 2009).[9] The adjusted NOAEC for non-cancer effects is 0.36 mg/m^3.

Perineal exposure to talc

The IARC has classified perineal use of talc-based body powder as "possibly carcinogenic to humans" (Group 2B) on the basis of limited evidence in humans. The analyzed case-control studies found a modest but consistent increase in risk, although bias and confounders could not be ruled out. The IARC Working Group concluded that, taken together, the epidemiological studies provide limited evidence in humans of an association between perineal use of talc-based body powder and an increased risk of ovarian cancer, although a minority of the Working Group considered the evidence inadequate because the exposure-response was inconsistent and the cohort analyzed did not support an association (IARC 2010).

The CIR Expert Panel (2013) determined that there is no causative relationship between cosmetic use of talc in the perineal area and ovarian cancer, and further concluded that talc is safe in the practices of use and concentration described in the CIR safety assessment. Issues noted by the CIR included a lack of consistent statistically significant positive associations across all studies; small risk ratio estimates; a failure to rule out other plausible explanations such as bias, confounders, and exposure misclassifications; and a lack of evidence from studies of occupational exposures and animal bioassays (CIR 2013; Fiume et al. 2015).

Animal studies

Rodents are poor experimental models for perineal studies for a number of reasons. Ovulation in rodents occurs only or mainly during the breeding season, and rodent ovaries are variously enclosed in an ovarian bursa in comparison to human ovaries. Ovarian epithelial tumours are also rare in these animals (Taher et al. 2018). Ovarian tumours do occur in some strains of mice and rats; however, the low incidence and/or the length of time required for the appearance of tumours renders them poorly feasible for experimental studies of ovarian carcinogenesis (Vanderhyden et al. 2003). On account of the limitations detailed above, in addition to the challenges posed by exposing animals via the perineal route, animal data are very limited; one single-dose study and one short-term repeated-dose study were available (Hamilton et al. 1984;

---

[9] This adjustment was made according to guidance and equations outlined in the U.S. EPA Supplemental Guidance for Inhalation Risk Assessment (US EPA 2009) and the U.S. EPA Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA 1994). Adjustment of duration to a continuous exposure scenario is done through the use of Equation 1 from U.S. EPA 2009 where the NOAEL[ADJ] = E × D × W, whereby the NOAEL[ADJ] (mg/m^3) = the no-observed adverse effect level (NOAEL) adjusted for the duration of the experimental regimen; E (mg/m^3) = the NOAEL or analogous exposure level observed in the experimental study; D (h/h) = the number of hours exposed/24 hours; and W (days/days) = the number of days of exposure/7 days. The NOAEC[ADJ] = 2 mg/m^3 × 6h/24h × 5d/7d = 0.36 mg/m^3

Keskin et al. 2009). No chronic or carcinogenicity animal studies on perineal exposure of talc were located in the literature.

A single injection of talc (in saline) into the bursa around the ovaries of rats showed foreign-body granulomas with confirmation of the presence of talc (Hamilton et al. 1984). Daily perineal or intravaginal application of talc (in saline) to rats for 3 months produced evidence of foreign-body reaction and infections; in addition, an increase in the number of inflammatory cells were found in all genital tissues. While no cancer or pre-cancer effects were observed, Keskin and colleagues (2009) noted that the study duration may have been too short to note these types of effects.

Human studies

Several meta-analyses of available epidemiological data have been published; some very recently (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2018). These studies have consistently reported a positive association with ovarian cancer and perineal talc exposure. Taher and colleagues (2018) identified 27 studies (24 case-control and 3 cohort) for a meta-analysis; ever versus never perineal use of talc and the risk of ovarian cancer resulted in a statistically significant pooled odds ratio (OR) of 1.28 (see Table 6-1). Other published meta-analyses have demonstrated similar results, with ORs ranging from 1.22 to 1.35 (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018).

Table 6-1. Available human epidemiological studies investigating the association of perineal use of talc and ovarian cancer (Taher et al. 2018, in preparation)

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
Case-control	686 (235)	Possible association in subgroup	Not included	Booth et al. 1989
Case-control	1014 (450)	Positive association	1.42 [1.08, 1.87]	Chang and Risch 1997
Case-control	336 (112)	Positive association in subgroup	Not included	Chen et al. 1992
Case-control	735 (313)	Positive association	1.60 [1.10, 2.33]	Cook et al. 1997
Case-control	430 (215)	Positive association	1.92 [1.27, 2.90]	Cramer et al. 1982
Case-control	4141 (2041)	Positive association	1.32 [1.15, 1.51]	Cramer et al. 2016
Case-control	3187 (1385)	Positive association	1.36 [1.14, 1.62]	Gates et al. 2008

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
Case-control	305 (153)	No association	2.49 [0.94, 6.60]	Godard et al. 1998
Case-control	1684 (824)	Positive association	1.30 [1.10, 1.54]	Green et al. 1997
Case-control	274 (116)	No association	1.10 [0.70, 1.73]	Harlow and Weiss 1989
Case-control	474 (235)	Positive association in subgroup	1.50 [1.00, 2.25]	Harlow et al. 1992
Case-control	306 (135)	No association	0.70 [0.40, 1.22]	Hartge et al. 1983
Case-control	2704 (902)	Positive association	1.40 [1.16, 1.69]	Kurta et al. 2012
Case-control	225 (46)	No association	1.15 [0.41, 3.23]	Langseth and Kjaerheim 2004
Case-control	3085 (1576)	Positive association in subgroup	1.17 [1.01, 1.36]	Merritt et al. 2008
Case-control	1354 (249)	Positive association in subgroup	1.37 [1.02, 1.84]	Mills et al. 2004
Case-control	2143 (1086)	No association	1.06 [0.85, 1.32]	Moorman et al. 2009
Case-control	2134 (767)	Positive association in subgroup	1.50 [1.10, 2.05]	Ness et al. 2000
Case-control	123 (77)	Possible association	1.00 [0.20, 5.00]	Rosenblatt et al. 1992
Case-control	2125 (812)	Possible association	1.27 [0.97, 1.66]	Rosenblatt et al. 2011
Case-control	1329 (584)	Positive association	1.44 [1.11, 1.87]	Schildkraut et al. 2016
Case-control	389 (189)	No association	1.05 [0.28, 3.94]	Tzonou et al. 1993
Case-control	727 (188)	Possible association	1.45 [0.81, 2.60]	Whittemore et al. 1988
Case-control	1155 (462)	No association	1.00 [0.80, 1.25]	Wong et al. 1999
Case-control	1297 (609)	Positive association	1.53 [1.13, 2.07]	Wu et al. 2009
Case-control	4092 (1701)	Positive association in	1.46 [1.27, 1.68]	Wu et al. 2015

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
		subgroup		
Cohort	108870 (797)	Possible association in subgroup	Not included	Gates et al. 2010
Cohort	78630 (307)	Possible association in subgroup	1.09 [0.86, 1.38]	Gertig et al. 2000
Cohort	41654 (154)	No association	0.73 [0.44, 1.21]	Gonzalez et al. 2016
Cohort	61285 (429)	No association	1.12 [0.92, 1.36]	Houghton et al. 2014

Abbreviation: CI, confidence interval.

Mode of action

The etiology of most ovarian tumours, in general, has not been well established. There are a number of different tumour types with characteristic histologic features, distinctive molecular signatures, and disease trajectories. Moreover, these tumours are heterogeneous, and they can arise from different tissues of the female reproductive tract, including the fallopian tube epithelium (National Academy of Sciences, Engineering, and Medicine 2016).

With respect to talc specifically, local chronic irritation leading to an inflammatory response is one possible mechanism of tumour progression that is frequently hypothesized (Muscat and Huncharek 2008; Penninkilampi and Eslick 2018; Taher et al. 2018). It is known that persistent indications of inflammation (including C-reactive protein, tumour necrosis factor, and other inflammatory markers) are detected in the blood of women prior to a diagnosis of ovarian tumours (Trabert et al. 2014). Increases in the number of inflammatory cells were found in all genital tissues of rats intravaginally exposed to talc for 3 months (Keskin et al. 2009). There is support for an association of inflammation and increased risk of ovarian cancer (National Academy of Sciences, Engineering and Medicine 2016; Rasmussen et al. 2017).

Talc particles were detected in the ovaries of rats that received intrauterine instillations of talc, and to a lesser extent in those that were dosed intravaginally with talc (Henderson et al. 1986). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications of talc to rabbits (Phillips et al. 1978) or to monkeys (Wehner et al. 1986).

Talc particles were identified in 10 of 13 human ovarian tumours but were also found in 5 of 12 "normal" ovarian tissues removed from patients with breast cancer (Henderson et al. 1971). Ovaries from 24 patients undergoing incidental oophorectomy were examined; 12 women reported frequent perineal talc use, and the other 12 women were

non-users. Talc particles were detected in all 24 cases (both ever- and non-users) (Heller et al. 1996b). Wehner (2002) attributed the talc in the never users to (a) possible sample contamination, because some studies using negative controls resulted in particle counts similar to the test sample; and/or (b) possible false positives due to the use of a single radioactive tracer. To explain why talc is present in the never users, Heller and colleagues (1996b) hypothesized that talc use during diapering could contribute to the ovarian particle burden.

Translocation of other inert particles, similar in size to talc, has also been studied. A study in monkeys did not show any translocation of carbon black particles when a suspension was placed in the vaginal posterior fornix (Wehner et al. 1985). However, retrograde migration was detected when rabbits were administered a lubricant powder intravaginally (Edelstam et al. 1997). Other authors have noted similar transportation of particles to the upper genital tract (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979). There are also some indications that particles can migrate from the vagina to the upper reproductive tract in humans (Egli and Newton 1961; Venter and Iturralde 1979; Heller et al. 1996a,b), and perineal exposure to talc has also been associated with a presence of talc in the lymph nodes and ovaries of women diagnosed with ovarian cancer (Heller et al. 1996a,b; Cramer et al. 2007).

Another possible mode of action that is hypothesized in the scientific literature is immune-mediated. It has been suggested that talc particles need not reach the ovaries but only need to reach the lower genital tract where talc could trigger changes (such as the production of heat shock proteins and/or decreased levels of antibodies) that could contribute to ovarian cancer (Cramer et al. 2005; Muscat et al. 2005). Human mucin 1 (MUC1) is expressed in high levels by ovarian cancer. Mucins are proteins involved in the formation of mucous barriers on epithelial surfaces (Gendler and Spicer 1995). Anti-MUC1 antibodies may have a protective effect; patients generate immunity against MUC1 produced by their tumours (Cramer et al. 2005). The Cramer et al. (2005) study used an enzyme-linked immunosorbent assay to measure anti-MUC1 antibody in women (controls; n = 721) to determine the factors that predict the presence of antibodies. It was found that the use of talc in the perineal area was associated with significantly decreased levels of antibodies to MUC1 (Cramer et al. 2005).

The most recent meta-analysis (Taher et al. 2018) employed the Hill criteria (Hill 1965) to assess the epidemiological evidence of a causal relationship. The Hill considerations are a set of factors (i.e., strength, consistency, specificity, temporality, biological gradient, biological plausibility, and coherence). These considerations form a framework for evaluating evidence in humans to help determine whether observed associations are causal (Hill 1965; Cogliano et al. 2004; US EPA 2005; Health Canada 2011; Fedak et al. 2015). Each factor, as reported in Taher et al. (2018), is elaborated upon below.

Strength: Of the 30 epidemiological studies examined by Taher et al. (2018), 15 case-control studies reported a positive association with statistical significance; 6 of these 15 had an OR of 1.5 or greater. Similarly, Penninkilampi and Eslick (2018) and Berge and colleagues (2018) each assessed 27 epidemiological studies and respectively

determined 14 and 13 case-control studies as reporting a positive association with statistical significance. In both cases, 5 of these studies had an OR of 1.5 or greater. Terry and colleagues (2013) only pooled 8 case-control studies; 5 of the 8 (63%) had a statistically significant positive association.

The individual cohort studies did not show a statistically significant association between perineal talc use and ovarian cancer (Berge et al 2018; Penninkilampi and Eslick 2018; Taher et al 2018). However, there was a positive association, with statistical significance, specific to invasive serous-type ovarian cancer in the cohort studies (OR = 1.25) (Penninkilampi and Eslick 2018). Given the long latency for ovarian cancer, the follow-up periods may not have been sufficient to capture all the cases for the individual cohort studies. Also, given the rarity of ovarian cancer, many of the available human studies may not be sufficiently powered to detect a low OR. Sample sizes were not large enough to detect a 20 to 30 % increase in risk; a group of over 200 000 women would need to be followed for over 10 years in order to detect a 20% (above background) increased risk with statistical significance (Narod 2016). With larger sample sizes, more individual studies may have demonstrated stronger associations.

Consistency: Several meta-analyses conducted over the past 15 years calculated similar ORs and resulted in similar conclusions; that there is a small yet consistent and statistically significant increased risk for ovarian cancer with perineal talc use (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al 2018). The epidemiological studies examined in these meta-analyses were conducted over different periods in time (across more than four decades), among different ethnicities, and spanned many geographical areas worldwide (Taher et al. 2018).

Specificity: Although there are many other risk factors for ovarian cancer (e.g., increased age, family history of cancer, obesity, nulliparity) (National Academy of Sciences, Engineering, and Medicine 2016), perineal talc exposure is specifically associated with cancer of the ovary and not other organs (Taher et al. 2018).

Temporality: In all case-control studies reporting positive outcomes, the participants recalled that exposure to talc preceded the reported outcome. However, in the cohort studies (reporting a lack of positive association), it is not known whether the follow-up period was adequate to detect a potential association between perineal talc exposure and ovarian cancer (Taher et al. 2018).

Biological gradient: There is a lack of an available exposure-effect relationship in the human epidemiological data. Many of the studies only assessed a single-dose level (ever versus never users). Furthermore, data with respect to the types of powder used by subjects or the amounts applied were not presented, and therefore a relationship between the concentration/dose of talc in the powder and the incidence of ovarian cancer could not be investigated. Taher and colleagues (2018) isolated seven studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc; however, none demonstrated both a clear dose-response

trend and statistical significance (Whittemore et al. 1988; Harlow et al. 1992; Mills et al. 2004; Wu et al. 2009; Rosenblatt et al. 2011; Cramer et al. 2016; Schildkraut et al. 2016).

Biological plausibility: Particles of talc are hypothesized to migrate into the pelvis and ovarian tissue, causing irritation and inflammation. The presence of talc in the ovaries has been documented (Heller et al. 1996b). This evidence of retrograde transport supports the biologic plausibility of the association between perineal talc application and ovarian exposure; however, the specific mechanism(s) and cascade of molecular events by which talc might cause ovarian cancer have not been identified (Taher et al. 2018).

Coherence: Multiple case-control studies reported a lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from the lower to the upper genital tract) and suppressed ovulation (as cited by Taher et al. 2018: Cramer et al. 1982, 2016; Whittemore et al. 1988; Rosenblatt et al. 1992; Green et al. 1997; Wong et al. 1999; Mills et al. 2004). As noted in Penninkilampi and Eslick (2018), the main reductions in cancer incidence with tubal ligation were for serous and endometrial tumour types but not for mucinous or clear-cell tumours. Thus, tubal ligation is only effective in reducing the incidence of the same tumour types noted to be associated with perineal talc use.

The most recent meta-analysis detailed above (Taher et al. 2018), and consistent with the Hill criteria, suggests a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc. Further, available data are indicative of a causal effect. A clear point of departure could not be derived from the available literature; consequently, hazard characterization is qualitative in nature.

6.2 Exposure assessment

This exposure assessment focuses on routes of exposure where critical effects have been identified; namely, non-cancer lung effects following inhalation of insoluble respirable particles of talc, and an association with ovarian cancer following perineal exposure to talc.

6.2.1 Environmental media, food and drinking water

Talc is a naturally occurring mineral, and there are several deposits in Canada (Kogel et al. 2006). Currently, there is one operating open-pit mine and concentrator along with an operating mill (MAC 2016); however, no talc concentration data in ambient air or around open-pit talc mines and processing facilities have been reported. Although particulate matter (PM) information for inhalable and respirable particles is available in the vicinity of these facilities (NPRI 2018), these data were not used in the exposure assessment as PM released from facilities is expected to contain a mixture of substances, hence the concentration would not reflect talc exposure from this source. However, given the

limited number of industrial and commercial sites producing and processing talc in Canada, talc exposure from ambient air is not expected to be significant.

Talc is insoluble in water (Table 3-1) and is expected to settle out during water treatment; exposure to the general population from drinking water is not expected.

There is potential for oral exposure resulting from the use of talc as a food additive; however, exposure from these uses is expected to be minimal (email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Exposure from the use of talc as a component in food packaging materials is expected to be negligible (email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Exposure from the oral route was not quantified because no critical health effects from the oral route of exposure have been identified. The JECFA has assigned an ADI of "not specified" for talc on the basis of low toxicity, and talc is "generally recognized as safe" as a food additive in the United States (JECFA 2006; U.S. FDA 2015).

6.2.2 Products available to consumers

Talc is present in approximately 8500 self-care products in Canada, including approximately 200 non-prescription drug products, approximately 2000 natural health products, and approximately 6500 cosmetic products. In addition, there are approximately 1300 prescription drugs containing talc. There is potential for oral exposure resulting from the use of self-care products and non-OTC drugs (including prescription, controlled substances, and ethical drugs) as a medicinal and non-medicinal ingredient containing talc. However, exposure from the oral route was not quantified as no critical health effects from the oral route of exposure have been identified.

There is the potential for dermal contact with talc from the use of self-care products. Systemic exposure resulting from dermal contact with talc is expected to be negligible as it is not expected that talc will be absorbed on the basis of its physical-chemical characteristics as an insoluble solid particle. In addition, a dermal health effect endpoint has not been identified for talc.

Notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, the LNHPD (modified 2018), the Drug Product Database (DPD), voluntary information submitted to Environment and Climate Change Canada and Health Canada (ECCC, HC 2017), publicly available databases and websites (e.g., Household Products Database 1993-; CPCat 2014; CPID 2017), and material safety and technical datasheets were used to identify products where there is: (a) the potential for inhalation of insoluble respirable talc, and (b) the potential exposure to the perineal region. These products and associated exposures are presented below.

No inhalation or perineal exposures were identified with respect to the major commercial or industrial uses of talc in paper, plastics, ceramics, and putties.

Inhalation exposure

For inhalation exposure, potential exposures were focused on products that were formulated as loose powders and were available to consumers, which included approximately 400 self-care products (primarily cosmetics). Products formulated as pressed powders, which comprise the majority of cosmetics containing talc (approximately 4000 products) were not identified as a potential source of exposure of concern because the formation of a "dust cloud" available for inhalation is not expected during the use of these products. Available information of interest were self-care products marketed as cosmetics, NHPs, or non-prescription drugs that are intended for application to the body, face, feet, buttocks (babies), and hair (e.g., dry hair shampoo). Concentrations of talc range from less than 10 to 100 % in these types of products.

In order to determine if talc loose-powder self-care products contain respirable particles, Health Canada measured the particle size distribution of three products (one baby powder and two adult body powder products) containing high concentrations of talc (>90%) available in Canada (Rasmussen 2017). Using an Aerodynamic Particle Sizer, the particle size distribution for the three products ranged from < 0.5 µm to 8 µm, with median particle sizes ranging from 1.7 to 2 µm. Thus, all of the particles were within the inhalable range (< 10 µm), and the median particle size was within the respirable range (< 4 µm). Number concentrations measured using a scanning mobility particle sizer indicated that the proportion of nano-sized particles (<100 nm) was small (< 10 %) to negligible, depending on the product.

Several studies were conducted by the cosmetic industry in the 1970s to provide data required to assess the safety of talc powder products and generate air concentrations (Aylott et al. 1979; Russell et al. 1979). These studies demonstrated that during the use of face, baby, and adult powders, there are quantifiable concentrations of respirable talc particles available for inhalation exposure. In 1978, Aylott and colleagues determined mean respirable air concentrations of 0.48 to 1.9 mg/m^3 of talc (< 7 µm) over 5 minutes for loose face powder, adult dusting powder, baby dusting powder, and micronized adult dusting powder. That same year, concentrations of talc (< 10 µm) of 0.19 mg/m^3 and 2.03 mg/m^3, respectively, were determined near the infant breathing zone during a simulation of routine application of talcum powder during diapering, and in the breathing zone of adults during the application of talcum powder to their body (Russell et al. 1979). In both of these studies, the highest air concentrations were associated with the adult application of talcum powder to their bodies over infant diapering and application of loose facial powder. There are uncertainties with the calculated talc concentrations determined from these studies due to limitations in the collection and analysis of talc concentrations on the basis of the use of older equipment, older sampling methods, and older talc products.

In 2017, a study assessing the health risk from the use of cosmetic talc from historical products was published (Anderson et al. 2017). This study included examining historical talc products from the 1960s and 1970s to characterize airborne respirable dust concentrations during the use of these products. To quantify respirable talc concentrations in the breathing zone, Anderson and colleagues (2017) designed a study where 5 volunteers were asked to apply historical talc products as they typically would in a bathroom setting. Cyclone air sampling devices were attached to the breathing zone of each volunteer. Each exposure simulation consisted of 8 application events, at six-minute intervals, for a total sampling duration of 48 minutes. This study design ensured that the sample mass on the sampling filter was large enough for quantification and accuracy, but it was not expected that during the typical use of a talc body powder that individuals apply talc every six minutes over a 48-minute window. Average talc concentrations over the 48-minute exposure simulation were calculated using the total measured mass (from 8 applications over 48 minutes) and the air volume over the entire 48-minute sampling period. Respirable talc concentrations ranged from 0.26 to 5.03 mg/m^3, and the average was 1.46 mg/m^3. The average air concentration by subject ranged from 0.44 to 3.28 mg/m^3. Respirable talc concentrations were more variable between subjects than within subjects, suggesting that individual behaviour has a strong influence in airborne concentrations.

In 2018, Health Canada conducted a small study in order to measure the air concentrations of particles in the breathing zone of adult volunteer subjects while they were applying talc-containing self-care products (Rasmussen 2018). Continuous, direct-reading, personal breathing-zone monitors (positioned beside the nose) measured average particulate matter of aerodynamic diameter of 4 µm or less (PM_4) concentrations of 0.48 ± 0.18 mg/m^3 and 1.80 ± 0.82 mg/m^3 for volunteers applying body powder and loose face powder, respectively. Subjects repeated the application in triplicate. These average concentrations fall within the range of concentrations measured by Anderson and colleagues (2017). In this study, the application of loose face powder resulted in the highest average air concentration in the immediate vicinity of the nose.

Several exposure scenarios were derived to characterize inhalation exposure to talc particles from the use of self-care products; namely, the use of baby, body, face, and foot powders (loose formulations), and dry hair shampoo. Average air concentrations by subject from Anderson et al. 2017 were combined with the body and face replicates from Rasmussen 2018 to obtain an overall average air concentration of 1.36 ± 0.97 mg/m^3. This value was used to estimate adjusted air concentrations for self-care products based on the highest concentration of talc present in these products. The results are summarized in Table 6-2. The inputs for each of these scenarios are outlined in Appendix A.

Table 6-2. Inhalation exposure estimates to talc from self-care products available to consumers

Product type	Age group	Concentration in air per event (mg/m^3)[a]	Adjusted exposure concentration (mg/m^3)[b]
Baby powder 100% talc	Infant and Adult	1.36	0.0071
Body powder 100% talc	Adult	1.36	0.0047
Face powder 100% talc	Adult	1.36	0.0047
Foot powder 97% talc	Adult	1.32	0.0034
Dry hair shampoo 100% talc	Adult	1.36	0.0011

[a] Average measured air concentrations (Anderson et al. 2017, Rasmussen 2018) × the highest concentration of talc in product type.
[b] Refer to Appendix A for details.

Perineal exposure

Several types of self-care products have the potential to result in exposure to the perineal region. There are several baby and body powders (approximately 50 products) with concentrations of talc that range from 0.3 to 100 %. There has been a decline in popularity of the use of talc for feminine hygiene practices over time; of 6000 North American women, 19 % of women born between 1920 and 1940 reported applying talc directly to the perineal region, but only 3% of women born after 1975 reported the same (Narod 2016). Houghton and colleagues (2014) reported that in 2001, the proportion of U.S. women who were users of perineal talc was estimated at 40 %, down from 52 % during 1993 to 1998.

There is a small number of diaper or rash cream self-care products (less than 10) which contains low concentrations of talc as a non-medicinal ingredient (up to 0.5 %). Talc is permitted as a medicinal ingredient in diaper rash products at concentrations from 45 to 100 % (Health Canada 2007); however, there are no diaper rash products listed in the LNHPD containing talc as a medicinal ingredient (LNHPD [modified 2018]).

Additional self-care products that have the potential for perineal exposure (approximately 100 products) include antiperspirants and deodorants (e.g., genital antiperspirants), body wipes, bath bombs, and to a lesser extent (due to wash off or removal) other bath products (i.e., soap, shower gel) and products associated with hair removal (e.g., epilatory products). These products are formulated as gels, sprays, loose powders, and solid cakes, and range in concentration from less than 1% to 100% talc.

As indicated in Section 4, there is no evidence to suggest that talc is currently being used as a dry lubricant on condoms or medical examination gloves in Canada. At present, these are not considered to be sources of perineal exposure.

As a quantitative point of departure could not be derived from the available literature, perineal exposure from the use of self-care products was not quantified.

6.3 Characterization of risk to human health

Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), no critical health effects were identified via the oral or dermal routes of exposure. As such, oral exposure to talc resulting from food intake and use of self-care products are not of concern.

Critical health effects have been identified following inhalation exposure to respirable talc particles. From the available toxicological studies, a NOAEC of 2 mg/m^3 from the NTP inhalation studies in mice and rats was identified in which non-cancer lung effects, with lung overload, were noted at the next highest concentration of 6 mg/m^3.

The average air concentration of talc following the use of a loose-powder self-care product (1.36 mg/m^3) provides a small margin of exposure (i.e., 1.5) to the NOAEC of 2 mg/m^3. However, the NOAEC is derived from a study with an exposure profile of 6 hours per day, 5 days per week, over 4 weeks, while the actual exposure scenarios from the use of self-care products are intermittent, occurring in minutes per day, daily, or weekly over many years. To address the differences in exposure between the NTP study and the actual use pattern, both the NOAEC and the talc air concentrations were adjusted to a continuous exposure scenario according to U.S. EPA guidance on inhalation risk assessment to more accurately characterize potential risk (U.S. EPA 1994, 2009). The NOAEC of 2 mg/m^3 is equivalent to an adjusted concentration of 0.36 mg/m^3, as noted in the Health Effects section. The NOAEC of 2 mg/m^3 was extracted from a 4-week inhalation study as a NOAEC for chronic exposure was not available. Episodic exposures from product use are expected to increase lung load due to the long alveolar clearance of talc. The adjusted air concentrations from the use of self-care products are presented in Table 6-3.

Table 6-3. Relevant exposure and hazard values for talc, and margins of exposure, for determination of risk

Exposure scenario	Adjusted air concentration, CA (mg/m^3)[a]	Adjusted critical-effect level (mg/m^3)	Critical health effect endpoint	MOE
Baby powder 100% talc	0.0071	NOAEC[adj]: 0.36	non-cancer lung effects	50

JNJTALC001094076

Body powder 100% talc	0.0047	NOAEC[adj]: 0.36	non-cancer lung effects	76
Face powder 100% talc	0.0047	NOAEC[adj]: 0.36	non-cancer lung effects	76
Foot powder 97% talc	0.0034	NOAEC[adj]: 0.36	non-cancer lung effects	106
Dry hair shampoo 100% talc	0.0011	NOAEC[adj]: 0.36	non-cancer lung effects	327

Abbreviations: adj, adjusted; CA, concentration in air per event; MOE, margin of exposure.
[a] From Anderson et al. (2017) and Rasmussen (2018), respectively, based on the highest concentration in products. For most of these product types, there is a wide range of talc concentrations (< 10 to 100 %).

The margins of exposure (MOEs) between the adjusted critical-effect level and the adjusted air concentrations range from 50 to 327 for self-care products. The MOEs for baby powder, body powder, face powder, and foot powder are considered potentially inadequate to account for uncertainties in the health effects (including a lack of a NOAEC from chronic studies) and exposure databases. The MOE for dry hair shampoo is considered adequate to address uncertainties in the health effects and exposure databases.

Based on available human data, ovarian cancer was also identified as a critical health effect for the perineal route of exposure to talc. There is the potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs). As noted in the Health Effects section, a point of departure cannot be derived for this health effect. Data from published meta-analyses of epidemiological studies indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2018). As noted by Narod (2016), "It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal." Similarly, Penninkilampi and Eslick (2018) noted that "the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association." Taher and colleagues (2018) noted that "consistent with previous evaluations by the International Agency for Research on Cancer (2010), and more recent and subsequent evaluations by individual investigators (Penninkilampi and Eslick 2018; Berge et al. 2018; Terry et al. 2013), the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans."

The meta-analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. Further, available data are indicative of a causal effect. Given that there is the potential for perineal exposure to talc from the use of various self-care products, a potential concern for human health has been identified.

6.4 Uncertainties in evaluation of risk to human health

The inhalation of talc has been associated with a variety of non-cancerous lung effects, commonly termed talcosis. Dose-response data for lung effects in humans is, for the most part, lacking, and the use of animal data to quantify risk due to talc inhalation is considered appropriate. Despite the lack of exposure quantification, there are numerous case reports, as well as worker studies, that have identified non-cancer health effects from inhalation of talc powders. There is some uncertainty regarding the extrapolation of the NOAEC identified in animal models exposed for 6 hours per day for a short duration (4 weeks) to long-term episodic human exposures. The true NOAEC for chronic exposure is likely substantially lower than 2 mg/m^3.

Some self-care products, in particular, some face powders, may contain a cover or another mechanism that would reduce the potential for the generation of a particle or dust cloud, or that would reduce the concentration of the dust cloud during use of the product. There is uncertainty as to which products, and the proportion of products on the market, that incorporate these exposure-mitigation measures.

There are limitations with the human epidemiological data. Potential sources of bias include selection bias due to low response rates or from limiting subjects, and exposure misclassification due to recall bias (Taher et al. 2018). Muscat and Huncharek (2008) also proposed that symptoms of ovarian cancer prior to diagnosis may increase the perineal use of talc and bias the results. However, Narod (2016) and Berge and colleagues (2018) put less emphasis on recall bias. In studies where the exposure is simple (e.g., never versus ever use), recall bias is unlikely to be an important source of bias (Narod 2016). The positive association is strongest for the serous histologic type (Berge et al. 2018; Taher et al. 2018); findings that the association may vary by histologic type detracts from the hypothesis of report bias, as this type of bias would likely operate for all histologic types (Berge el al. 2018).

Ovarian cancer, in general, is not well understood (National Academy of Sciences, Engineering, and Medicine 2016), and a comparable animal model is not available. Health Canada has identified self-care products with the potential for perineal exposure (e.g., baby powder, body powders, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs); however, there is no indication exactly how the products are being used, the extent to which they would contribute to perineal exposure, and with what frequency and amount.

Talc use during diapering is a confounder that was not adequately accounted for in the epidemiological studies. It has not been determined whether the internal female genital

tract is exposed to talc dusts during infancy (Muscat and Huncharek 2008). As well, not all the available human studies are clear as to the formulations used for perineal applications. It is possible that the identified cancer incidences are specific to loose-powder formulations; however, there is inadequate information to attribute the cancer incidences to other formulation types (e.g., creams).

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from talc. It is proposed to conclude that talc does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that talc meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that talc meets one of the criteria set out in section 64 of CEPA.

Talc is proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

References

Akira M, Kozuka T, Yamamoto S, Sakatani M, Morinaga K. 2007. Inhalational talc pneumoconiosis: radiographic and CT findings in 14 patients. Am J Roentgenol. 188(2):326-333.

Anderson EL, Sheehan PJ, Kalmes RM, Griffin JR. 2017. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Anal. 37(5):918-928.

Aylott RI, Byrne GA, Middleton JD, Roberts. 1979. Normal use levels of respirable cosmetic talc: preliminary study. Int J Cosmet Sci. 1:177-186.

Berge W, Mundt K, Luu H, Boffetta P. 2018. Genital use of talc and risk of ovarian cancer: a meta-analysis. Eur J Cancer Prev. 27(3):248-257.

Booth M, Beral V, Smith P. 1989. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 60(4):592-598.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C. 1999, c.33. Canada Gazette Part III, vol. 22, no. 3.

Carr CJ. 1995. Talc: Consumer Uses and Health Perspectives. Proceedings of a workshop. Bethesda, Maryland, January 31–February 1, 1994. Regul Toxicol Pharmacol. 21(2):211-215.

Cevc G. 1997. Drug delivery across the skin. Expert Opin Inv Drug. 6(12):1887-1937.

Chang S, Risch HA. 1997. Perineal talc exposure and risk of ovarian carcinoma. Cancer. 79(12):2396-2401.

Chang CJ, Tu YK, Chen PC, and Yang HY. 2017. Occupational exposure to talc increases the risk of lung cancer: A meta-analysis of occupational cohort studies. Can Respir J. 2017:1-12.

ChemIDplus [database]. 1993-. Bethesda (MD): U.S. National Library of Medicine. [updated 2017 April 11; accessed 2017 May 26].

Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. 1992. Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol. 21(1):23-29.

[CIMT] Canadian International Merchandise Trade Database [database]. 2017. Ottawa (ON): Government of Canada. [accessed 2017 October].

[CIR] Cosmetic Ingredient Review Expert Panel. 2013. Safety Assessment of Talc as Used in Cosmetics. Final Report [PDF]. Washington (DC): Cosmetic Ingredient Review. [accessed 2017 November].

Cogliano VJ, Baan RA, Straif K, Grosse Y, Secretan MB, Ghissassi FE, Kleihues P. 2004. The science and practice of carcinogen identification and evaluation. Environ Health Perspect. 112(13):1269-1274.

Cook LS, Kamb ML, Weiss NS. 1997. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol. 145(5):459-465.

[CPCat] Chemical and Product Categories [database]. 2014. Ver. 04. Washington (D.C.): U.S. Environmental Protection Agency. [updated 2014 May 21; accessed 2014 Nov 21]. [Database described

in Dionisio KL, Frame AM, Goldsmith MR, Wambaugh JF, Liddell A, Cathey T, Smith D, Vail J, Ernstoff AS, Fantke P, et al. 2015. Exploring consumer exposure pathways and patterns of use for chemicals in the environment. Toxicol Rep. (2):228-237.].

[CPID] Consumer Product Information Database [database]. 2017. McLean (VA): DeLima Associates. [accessed 2017 Nov 21].

Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. 2016. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. Epidemiology. 27(3):334-346.

Cramer DW, Welch WR, Berkowitz RS and Godleski JJ. 2007. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long term genital exposure to cosmetic talc. Obstet Gynecol. 110(2 Pt 2):498-501.

Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, Finn OJ. 2005. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-1131.

Cramer DW, Welch WR, Scully RE, Wojciechowski CA. 1982. Ovarian cancer and talc: a case-control study. Cancer. 50(2):372-376.

Cruthirds TP, Cole FH, Paul RN. 1977. Pulmonary talcosis as a result of massive aspiration of baby powder. South Med J. 70(5):626-628.

[CTFA] Cosmetic, Toiletry and Fragrance Association. 1983. Summary for the Results of Surveys of the amount and Frequency of use of cosmetic products by Women. Report Prepared by Pitkin B, Rodericks JV, Turnbull D. Washington (DC): CTFA Inc.

[Danish EPA] Danish Environmental Protection Agency. 2016. Evaluation of health hazards by exposure to talcum, cosmetic grade (non-fibrous) and proposal of a health-based quality criterion for ambient air [PDF]. Denmark: Danish Environmental Protection Agency. ISBN: 978-87-93529-23-6.

De Boer CH. 1972. Transport of particulate matter through the human female genital tract. J Reprod Fertil. 28(2):295-297.

Douglas A, Karov J, Daka J, Hinberg I. 1998. Detection and Quantitation of Talc on Latex Condoms. Contraception. 58(3):153-155.

[DPD] Drug Product Database [database]. [modified 2018 June 12]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 15].

Environment Canada. 2013. DSL Inventory Update data collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain substances on the Domestic Substances List*. Data prepared by: Environment Canada, Health Canada; Existing Substances Program.

[ECCC] Environment and Climate Change Canada. 2018. Science approach document: ecological risk classification of inorganic substances. Ottawa (ON): Government of Canada.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2017. Targeted information gathering for screening assessments under the Chemicals Management Plan (February to July 2017). Data prepared by: ECCC, Health Canada; Existing Substances Program.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Mar 12]. Categorization of chemical substances. Ottawa (ON): Government of Canada. [accessed 2018 Aug 30].

Edelstam GAB, Sjösten ACE, Ellis, H. 1997. Retrograde migration of starch in the genital tract of rabbits. Inflammation. 21(5):489-499.

Egli GE, Newton M. 1961. The transport of carbon particles in the human female reproductive tract. Fertil Steril. 12:151-155.

[EU] Commission of the European Communities. [modified 2001 Oct 1]. Report from the Commission on Dietary Food Additive Intake in the European Union. Brussels (BE): Commission of the European Communities.

[EuroTalc] Scientific Association of European Talc Producers. 2017. "What is talc?" Brussels (BE): Eurotalc. [accessed 2017 May 29]

[FAO] Food and Agriculture Organization of the United Nations. 2006. Combined Compendium of Food Additives Specifications: Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. FAO Food and Nutrition Paper 52.

Fedak KM, Bernal A. Capshaw ZA, Gross S. 2015. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 12:14.

Feigin DS.1986.Talc: understanding its manifestations in the chest. Am J Roentgenol. 146(2):295-301.

Fiume MM, Boyer I, Bergfeld WG, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks Jr JG, Shank RC, Slaga TH, Snyder PW, Anderson FA. 2015. Safety Assessment of Talc Used in Cosmetics. Int J Toxicol. 34(1 suppl):66S-129S.

Frank C, Jorge L. 2011. An uncommon hazard: Pulmonary talcosis as a result of recurrent aspiration of baby powder. Respir Med CME. 4(3):109-111.

Ficheux AS, Wesolek N, Chevillotte G, Roudot AC. 2015. Consumption of cosmetic products by the French population. First part: Frequency data. Food Chem Toxicol. 78:159-169.

Frosch PJ, Kligman AM. 1976. The chamber-scarification test for irritancy. Contact Derm. 2:314-324.

Gates MA, Tworoger SS, Terry KL, Titus-Ernstoff L, Rosner B, De Vivo I, Cramer DW, Hankinson SE. 2008. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 17(9):2436-2444.

Gates MA, Rosner BA, Hecht JL, Tworoger SS. 2010. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 171(1):45-53.

Gendler SJ, Spicer AP. 1995. Epithelial mucin genes. Annu Rev Physiol. 57:607-634.

Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE. 2000. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 92(3):249-252. Nursing Health Study

Gibbs AE, Pooley FD, Griffiths DM, Mitha R, Craighead JE, Ruttner JR. 1992. Talc pneumoconiosis: a pathologic and mineralogic study. Hum Pathol. 23(12):1344-1354.

Gibel W, Lohs K, Horn KH, Wildner GP, Hoffmann F. 1976. Experimental study on cancerogenic activity of asbestos filters. Arch Geschwulstforsch. 46:437-442.

Godard B, Foulkes WD, Provencher D, Brunet JS, Tonin PN, Mes-Masson AM, Narod SA, Ghadirian P. 1998. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. Am J Obstet Gynecol. 179(2):403-410.

Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. 2016. Douching, talc use, and risk of ovarian cancer. Epidemiology. 27(6):797-802.

Gould SR, and Barnardo DE. 1972. Respiratory distress after talc inhalation. Brit J Dis Chest. 66:230-233.

Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B. 1997. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int Cancer. 71(6):948-951.

Gysbrechts C, Michiels E, Verbeken E, Verschakelen J, Dinsdale D, Nemery B, Demedts M. 1998. Interstitial lung disease more than 40 years after a 5 year occupational exposure to talc. Eur Respir J. 11(6):1412-1415.

Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K. 1984. Effects of talc on the rat ovary. Br J Exp Pathol. 65(1):101-106.

Harlow BL, Weiss NS. 1989. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol. 130(2):390-394.

Harlow BL, Cramer DW, Bell DA, Welch WR. 1992. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol. 80(1):19-26.

Hartge P, Hoover R, Lesher LP, McGowan L. 1983. Talc and ovarian cancer. J Am Med Assoc. 250(14):1844.

Health Canada. 2007. Diaper rash products [PDF]. Ottawa (ON): Government of Canada.

Health Canada. 2010. PMRA list of formulants [PDF]. Ottawa (ON): Government of Canada.

Health Canada. 2011. Weight of evidence: general principles and current applications at Health Canada. November 2011. Unpublished report. Prepared by the Task Force on Scientific Risk Assessment's Weight of Evidence Working Group.

Health Canada. 2015. Natural Health Product Traditional Chinese Medicine Ingredients (TCMI). Ottawa (ON): Government of Canada.

Health Canada. [modified 2017 May 3]. List of permitted food additives. Ottawa (ON): Government of Canada. [accessed 2017 May 29].

Health Canada. [modified 2018 Jun 14]. Cosmetic ingredient hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Government of Canada. [accessed 2018 Aug 30].

Heller DS, Gordon RE, Westhoff C, Gerber S. 1996a. Asbestos exposure and ovarian fiber burden. Am J Ind Med. 29:435-439.

Heller DS, Westhoff C, Gordon RE, Katz N. 1996b. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol. 174(5):1507-1510.

Henderson WJ, Joslin CAF, Griffiths K, Turnbull AC. 1971. Talc and carcinoma of the ovary and cervix. BJOG: Int J Obstet Gynaecol. 78(3):266-272.

Henderson WJ, Hamilton TC, Baylis MS, Pierrepoint CG, Griffiths K. 1986. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res. 40(2):247-250.

Hill AB. 1965. The environment and disease: association or causation? Proc R Soc Med. 58:295-300.

Hollinger MA. 1990. Pulmonary toxicity of inhaled and intravenous talc. Toxicol Lett. 52(2):121-127; discussion 117-119.

Houghton SC, Reeves KW, Hankinson SE, Crawford L, Lane D, Wactawski-Wende J, Thomson CA, Ockene JK, Sturgeon SR. 2014. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst. 106(9). Women's Health Initiative

Household Products Database [database]. 1993-. Bethesda (MD): National Library of Medicine (US). [updated 2016 September; accessed 2017 June 19].

[HSDB] Hazardous Substances Data Bank [database]. 2005. CAS RN 14807-96-6. Bethesda (MD): National Library of Medicine (US). [complete update 2005 May 2; accessed 2017 Nov 21].

Huncharek M, Geschwind JF, Kupelnick B. 2003. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Research 23(2C):1955-1960.

[IARC] International Agency for Research on Cancer. 1987. Talc not containing asbestiform fibres (group 3). Talc containing asbestiform fibres (group 1). Summaries & Evaluations. Suppl 7:349.

[IARC] International Agency for Research on Cancer. 2010. Carbon Black, Titanium Dioxide, and Talc, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 93:277-413.

[ISO] International Organization for Standardization. 2015. ISO 4074: 2015 Natural rubber latex male condoms – Requirements and test methods. Geneva (CH): International Organization for Standardization.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2006. Compendium of Food Additive Specifications. FAO JECFA Monograph 1.

Keskin N, Teksen YA, Ongun EG, Ozay Y, Saygili H. 2009. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Arch Gynecol. 280(6):925-931.

Kogel JE, Trivedi NC, Barker JM, Krukowski ST, eds. 2006. Industrial Minerals and Rocks. 7th ed. Littleton (CO): Society for Mining, Metallurgy, and Exploration, Inc.

Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, Modugno F, Ness RB, Diergaarde B. 2012. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. Cancer Epidemiol Biomarkers Prev. 21(8):1282-1292.

Langseth H, Kjærheim K. 2004. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scand J Work Environ Health. 30(5):356-361.

Langseth H, Hankinson SE, Siemiatycki J, Weiderpasse E. 2008. Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health. 62(4):358-360.

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2018 Feb 6]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 14].

Lundberg M, Wrangsjo K, Johansson SGO. 1997. Latex allergy from glove powder – an unintended risk with the switch from talc to cornstarch. Allergy 52:1222-1228.

[MAC] Mining Association of Canada. 2016. Facts and Figures of the Canadian Mining Industry F&F 2016 [PDF]. [accessed 2017 Nov 21].

[MAK-Commission] The MAK Collection for Occupational Health and Safety. 2012. Talc (without asbestos fibres) (respirable fraction). Weinheim (DE): Wiley-VCH Verlag GmbH & Co. KGaA. The MAK-collection Part I: MAK Value Documentations, Vol. 22. 226-279.

Marchiori E, Lourenço S, Gasparetto TD, Zanetti G, Mano CM, Nobre LF. 2010. Pulmonary talcosis: imaging findings. Lung. 188(2):165-171.

Merritt MA, Nagle CM, Webb PM, Bowtell D, Chenevix-Trench G, Green A, DeFazio A, Gertig D, Traficante N, Moore S, et al. 2008. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer. 122(1):170-176.

Mills PK, Riordan DG, Cress RD, Young HA. 2004. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer. 112(3):458-464.

Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. 2009. Ovarian cancer risk factors in African-American and white women. Am J Epidemiol. 170(5):598-606.

Muscat JE, Huncharek, MS. 2008. Perineal talc use and ovarian cancer: a critical review. Eur J Cancer Prev. 17(2):139-146.

Muscat J, Huncharek M, Cramer DW. 2005. Talc and anti-MUC1 antibodies. Cancer Epidemiol Biomarkers Prev. 14(11 Pt. 1):2679.

Narod SA. 2016. Talc and ovarian cancer. Gynecol Oncol. 141:410-412.

National Academy of Sciences, Engineering, and Medicine. 2016. Ovarian cancers: evolving paradigms in research and care. Washington (D.C.): National Academy Press.

Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. 2000. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11(2):111-117.

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2018 July 6]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 14].

[NIOSH] National Institute for Occupational Safety and Health (US). 2014. Talc (silica and fibre free). International Chemical Safety Card (ICSC). Atlanta (GA): Centre for Disease Control. ICSC # 0329. [accessed 2018 Mar].

[NPRI] National Pollutant Release Inventory. 2018. NPRI Datasets: Substance: PM10 - Particulate Matter <= 10 Microns, Company/Facility information: Imerys Talc Canada Inc. (2017). Ottawa (ON): Government of Canada. Search results for PM_{10} at Imerys Talc Canada Inc. [updated 2018 June 14].

[NTP] National Toxicology Program. 1993. NTP technical report on the toxicology and carcinogenesis studies of talc (CAS NO. 14807-96-6) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park (NC): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. National Toxicology Program, NTP TR 421, NIH Publication No. 93-3152.

Oberdorster G. 1995. The NTP talc inhalation study: a critical appraisal focussed on lung particle overload. Regul Toxicol Pharmacol. 21(2):233-241.

[OECD] Organisation for Economic Co-operation and Development Screening Information Dataset (SIDS). 2004. Synthetic Amorphous Silica and Silicates. SIDS Initial Assessment Report for SIAM 19 [PDF]. Berlin (DE): UNEP Publications. [accessed 2018 Sept].

[OSHA] Occupational Safety and Health Administration. 1999. Talc (not containing asbestos). Chemical Sampling Information. Washington (DC): Occupational Safety and Health Administration (US). [accessed 2017 Nov 7].

Patarino F, Norbedo S, Barbi E, Poli F, Furlan S, Savron F. 2010. Acute Respiratory Failure in a Child after Talc Inhalation. Respiration. 79:340.

Penninkilampi R, Eslick GD. 2018. Perineal talc use and ovarian cancer: A systemic review and meta-analysis. Epidemiology. 29(1):41-49.

Phillips JC, Young PJ, Hardy K, Gangolli SC.1978. Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. Food Cosmet Toxicol.16(2):161-163.

Pickrell JA, Snipes MB, Benson JM, Hanson RL, Jones RK, Carpenter RL, Thomspon JJ, Hobbs CH, Brown SC. 1989. Talc deposition and effects after 20 days of repeated inhalation exposure of rats and mice to talc. Environ Res. 49:233-245.

Ramlet AA. 1991. A rare complication of ambulatory phlebectomy. Talc Granuloma (French). Phlébologie 44:865-871.

Rasmussen CB, Kjaer SK, Albieri V, Bandera EV, Doherty JA, Høgdall E, Webb PM, Jordan SJ, Rossing MA, Wicklund KG, Goodman MT, Modugno F, Moysich KB, Ness RB, Edwards RP, Schildkraut JM, Berchuck A, Olson SH, Kiemeney LA, Massuger LF, Narod SA, Phelan CM, Anton-Culver H, Ziogas A, Wu AH, Pearce CL, Risch HA, Jensen A; on behalf of the Ovarian Cancer Association Consortium. 2017. Pelvic inflammatory disease and the risk of ovarian cancer and borderline ovarian tumors: a pooled analysis of 13 case-control studies. Am J Epidemiol. 185(1):8-20.

Rasmussen P. 2017. Preliminary talc exposure results. Dec 29, 2017. Unpublished Report Ottawa (ON): Exposure and Biomonitoring Division, Health Canada.

Rasmussen P. 2018. Respirable (PM4) particle concentrations in air while using cosmetics containing talc in Canada, First draft Data Report. July 25, 2018. Unpublished report. Ottawa (ON): Exposure and Biomonitoring Division, Health Canada.

Rosenblatt KA, Szklo M, Rosenshein NB. 1992. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol. 45(1):20-25.

Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. 2011. Genital powder exposure and the risk of epithelial ovarian cancer. Cancer Causes Control. 22(5):737-742.

Russell RS, Merz RD, Sherman WT, Sivertson JN. 1979. The determination of respirable particles in talcum powder. Cosmet Tox. 17(2):117-122.

Schildkraut JM, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy ML, Cote ML, Funkhouser E, Peres LC, Peters ES, et al. 2016. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). Cancer Epidemiol Biomarkers Prev. 25(10):1411-1417.

SDS Search Tool [database]. 2016. Ottawa (ON): Government of Canada. [updated 2016 Sept 15; accessed 2017 Nov 22]. [restricted access].

Shakoor A, Rahatullah A, Shah AA, Zubairi ABS. 2011. Pulmonary talcosis 10 years after brief teenage exposure to cosmetic talcum powder. BMJ Publishing Group. BMJ Case Reports. 2011:bcr0820114597.

Simsek F, Turkeri L, Ilker Y, Kullu S, Akdas A. 1992. Severe obstruction of the urinary tract due to talcum powder granuloma after surgery. A case report. Int Urol Nephrol. 24:31-34.

Statistics Canada. 2016. Data Tables, 2016 Census. Census family structure including stepfamily status (9) and number and age combinations of children (29) for census families with children in private households of Canada, Provinces and Territories, census metropolitan areas and census agglomerations, 2016 and 2100 censuses – 100% data. Ottawa (ON): Government of Canada. [accessed 2017 Nov 23].

Taher MK, Farhat N, Karyakina N, Shilnikova N, Ramoju S, Gravel CA, Krishnan K, Mattison D, Krewski D. 2018. Systematic review of the association between perineal use of talc and ovarian cancer risk. [in preparation].

Terry KL, Karageorgi S, Shvetsov YB, Merritt MA, Lurie G, Thompson PJ, Carney ME, Weber RP, Akushevich L, Lo-Ciganic WH, et al. 2013. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev Res. 6(8):811-821.

Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, Brinton LA, Pfeiffer RM, Shields MS, Chaturvedi AK, Hildesheim A, and Wentzensen N. 2014. Pre-diagnostic serum levels if inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. Gynecol Oncol. 135(2):297-304.

Tukiainen P, Nickels J, Taskinen E, Nyberg M. 1984. Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis? Bri J Ind Med. 41:84-87.

Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. 1993. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer. 55(3):408-410.

United States. 2016. Federal Register. Banned Devices; Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove. A Rule by the Food and Drug Administration on 12/19/2016. US: Federal Register (US). Vol. 81, No. 243. 21 CFR 878. p. 91722-91731 [accessed 2018 Jan 3].

[U.S. EPA] United States Environmental Protection Agency. 1992. Health Assessment Document for Talc. Washington (D.C.): Office of Research and Development. Report No. EPA 600/8-91/217.

[U.S. EPA] United States Environmental Protection Agency. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Research Triangle Park (NC): U.S. EPA, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development.

[U.S. EPA] United States Environmental Protection Agency. 2005. Guidelines for Carcinogen Risk Assessment [PDF]. Washington (D.C.): U.S. EPA, EPA/630/P-03/001F.

[U.S. EPA] United States Environmental Protection Agency. 2009. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment). Washington (D.C.): U.S. EPA, Office of Superfund Remediation and Technology Innovation.

[U.S. EPA] United States Environmental Protection Agency. 2011. Exposure Factors Handbook 2011 Edition (Final Report). Washington (D.C.): U.S. EPA, EPA/600/R-09/052F.

[U.S. FDA] United States Food and Drug Administration. 2015. Select Committee on GRAS Substances (SCOGS) Opinion: Silicates. Silver Spring (MD): U.S. Food and Drug Administration. [accessed 2018 Aug 17]

[U.S. FDA] United States Food and Drug Administration. 2016. About the GRAS Notification Program. Silver Spring (MD): US Food and Drug Administration. [accessed 2017 Mar 12].

[USGS] United States Geological Survey. 2000. U.S. Talc-Baby Powder and Much More [PDF]. Reston (VA): US Geological Survey. USGS Fact Sheet FS-065-00. [accessed 2017 May 29].

[USGS] United States Geological Survey. 2018. Mineral Commodity Summaries. Talc and Pyrophyllite [PDF]. Reston (VA): US Geological Survey. [accessed 2018 August 13].

[USP] US Pharmacopeia. 2011. USP Monographs: Talc. Talc Revision Bulletin Official August 1, 2011 [PDF]. US: The United States Pharmacopeial Convention. [accessed 2018 May 3].

Vallyathan NV, Craighead JE.1981. Pulmonary pathology in workers exposed to nonasbestiform talc. Hum Pathol.12(1):28-35.

Vanderhyden BC, Shaw TJ, Ethier JF. 2003. Animal models of ovarian cancer. Reprod Biol Endocrinol. 1:67.

Venter PF, Iturralde M. 1979. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. S Afr Med J. 55(23):917-919.

Wadaan MAM. 2009. Effects of repeated exposure to talcum powder on rabbit skin. Indian J Appl Pure Biol. 24(1):111-115.

Wagner JC, Berry G, Cooke TJ, Hill RJ, Pooley FD, Skidmore JW. 1977. Animal experiments with talc. Inhaled Particles. 4 Pt 2:647-654.

Warheit, DB, Kreiling R, Levy LS. 2016. Relevance of the rat lung tumor response to particle overload for human risk assessment-Update and interpretation of new data since ILSI 2000. Toxicology. 374:42-59.

Wehner AP, Tanner TM, Buschbom RL. 1977a. Absorption of ingested talc by hamsters. Food Cosmet Toxicol.15(5):453-455.

Wehner AP, Wilkerson CL, Cannon WC, Buschbom RL, Tanner TM. 1977b. Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. Food Cosmet Toxicol.15(5):213-224.

Wehner AP, Hall AS, Weller RE, Lepel EA, Schirmer RE. 1985. Do particles translocate from the vagina to the oviducts and beyond? Food Chem Toxicol. 23(3):367-372.

Wehner AP, Weller RE, Lepel EA. 1986. On talc translocation from the vagina to the oviducts and beyond. Food Chem Toxicol. 24(4):329-338.

Wehner AP. 2002. Cosmetic talc should not be listed as a carcinogen: comments on NTP's deliberations to list talc as a carcinogen. Regul Toxicol Pharmacol. 36:40-50.

Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, Jung DL, Ballon S, Hendrickson M. 1988. Personal and environmental characteristics related to epithelial ovarian cancer. I. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol. 128(6):1228-1240.

[WHO, UNFPA, FHI] World Health Organization, United Nations Population Fund, Family Health International. 2013. Male latex condom. Specification, prequalitfication and guidelines for procurement, 2010, revised April 2013. Geneva (CH): World Health Organization. [accessed 2017 Dec 20].

Wild P, Leodolter K, Refregier M, Schmidt H, and Bourgkard E. 2008. Effect of talc dust on respiratory health: results of a longitudinal survey of 378 French and Austrian talc workers. Occup Environ Med. 65: 261-267.

Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol. 93(3):372-376.

Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. 2009. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-1415.

Wu AH, Pearce CL, Tseng CC, Pike MC. 2015. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-1100.

Zazenksi R, Ashton WH, Briggs D, Chudkowski M, Kelse JW, MacEachern L, McCarthy EF, Norhauser MA, Roddy MT, Teetsel NM, Wells AB, Gettings SD. 1995. Talc: Occurrence, Characterization, and Consumer Applications. Reg Pharm Tox. 21:218-229.

Appendix A. Inhalation exposure estimates

Table A-1. Estimated inhalation exposure concentrations from self-care products containing loose powder talc available to consumers

Scenario	Talc product conc.[a]	Study[b] conc. (mg/m³)	CA[b] (mg/m³)	ET[c] (hr/d)	EF[d] (d/yr)	ED[e] (yr)	EC adjusted (mg/m³)[b]
Baby powder, infants	100 %	1.36	1.36	0.125	365	4	0.0071
Baby powder, adults	100 %	1.36	1.36	0.125	365	8	0.0071
Body powder, adults	100 %	1.36	1.36	0.083	365	58	0.0047
Face powder, adults	100 %	1.36	1.36	0.083	365	58	0.0047
Foot powder, adults	97 %	1.36	1.32	0.083	274	58	0.0034
Dry hair shampoo, adults	100 %	1.36	1.36	0.083	84	58	0.0011

Abbreviations: Conc., concentration; CA, concentration in air per event; ET, exposure time; EF, exposure frequency; ED, exposure duration; EC, adjusted exposure concentration.

[a] Highest concentration of talc found per product type from notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, DPD [modified 2018], email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenced; LNHPD [modified 2018], email from the Non-prescription and Natural Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenced; Fiume et al. 2015; Household Product Database 1993-; CPCat 2014; CPID 2017; SDS Search Tool 2016.

[b] Average by subject from Anderson et al. 2107 and Rasmussen 2018 (unpublished). CA = average study concentration × maximum talc concentration in product.

[c] ET is 5 minutes/application based on median time spent in the bathroom following a shower or bath (U.S. EPA 2011) × number of applications/day, whereby baby powder assumes 1.5 applications/day (CTFA 1983); the rest assume 1 application/day.

[d] EF is assumed to be daily for baby, body (U.S. EPA 2011) and face powder (Ficheux et al. 2015); foot powder 0.75 times/day or 274 times/year (Ficheux et al. 2015); dry hair shampoo 0.23 times/day or 84 times/year (Ficheux et al. 2015).

[e] Assumed infant wears diapers up to 4 years, adult exposure to baby powder from diapering children, 4 years per child and assume 2 children per family (Statistics Canada 2016), adult exposure for body powder, and foot powder (80 years lifetime, 12 years child).

[f] Adjusted exposure concentration is calculated as per Equation 8 in the U.S. EPA 2009 guidance document "Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual," where EC = (CA × ET × EF × ED)/AT, and AT = averaging time, which is on the basis of ED × 365 days/year × 24 hours/day.

Exhibit 101

Johnson & Johnson

return to

New Brunswick, N.J.
December 3, 1975

Subject: Talc in the Ovaries

Dr. D. R. Petterson

Attached is a letter received from Dr. Keith Griffiths, who is Director of the Tenovus Institute for Cancer Research in Cardiff. The letter arrived in response to a small donation I had sent the Cardiff Scientific Society with the main objective of trying to determine what research is in actual fact being conducted at the Tenovus Institute.

It might be of value to identify the precise scientific data available to Tenovus concerning talc and ovarian cells. We are not budgeted to support the research outlined and shall so inform Griffith if this meets with your approval.

Gavin Hildick-Smith

GHS/cd
Att.

cc:
Mr. G. Lee
Dr. F. R. Rolle
Dr. B. Semple

G. Lee,

It would be wise to know ahead of time, just what Gavin intends doing. Did you know he was planning to donate to the C.S.S.? It has certainly given supposedly the opening to prod us on notices re the talc/ovary problem.

Don.

No — we were not asked. We shall discuss this at the advisory group meeting.
Jim.

Exhibit 102

~~RES~~
~~GHD~~
HRC
DJ

Johnson & Johnson

JAN 25 REC'D
FEB 14 REC'D

New Brunswick, N.J.

January 18, 1974

Subject: Talc/Asbestos
Meeting with Commissioner Schmidt, FDA
January 16, 1974

Memo to File

Attendees:

for FDA: Dr. V. Wodicka, Director, Bureau of Foods
Dr. H. Eiermann,* Director, Division of Cosmetics Technology.
Mr. J. Wenninger, Deputy Director, Division of Cosmetics Technology.

Later: Commissioner Schmidt and the above.

for J&J: Dr. R. Fuller, Dr. G. Hildick-Smith, Dr. W. Nashed

A preliminary meeting with Dr. Wodicka and his staff was held. We traced the history of the talc/asbestos problem: Kretchmer letter; FDA Symposium, August, 1971, where Mt. Sinai people admitted that their analysis based on optical microscopy of our product was wrong and that Johnson & Johnson Baby Powder was the best talc available; and we mentioned the voluminous data which we had shared with the FDA. Dr. Eiermann and Mr. Wenninger corroborated our presentations to Dr. Wodicka.

Hmmmm.

Dr. Eiermann then said that he has reviewed the CTFA Round-Robin test results with his microscopist, Mr. Schulze, and said that Mr. Schulze still thinks the method is valid. We pointed out that we believe that the method has some basic flaws as outlined in the CTFA comment; however, we believe that a cooperative program between FDA and industry should result in a practical solution to the problem.

* Former J&J employee in Brazil.

Plaintiff's Exhibit No. P-660

We pointed out that we had developed a DTA method capable of measuring 1% chrysotile and we also believe that a step scan x-ray method can be used to detect 0.2% tremolite.

Dr. Eiermann said that they have obtained DTA equipment and x-ray equipment and that he has some reservation about allowing 1% chrysotile.

We volunteered to cooperate with his scientists in the development of the method for DTA and promised to provide a copy of a proposed publication regarding this method.

Dr. Eiermann said that his main interest at this time is to find what level of dust exposure occurs in the process of dusting a baby and that they would like to use the data to calculate allowable asbestos using 5 fibers per ml (OSHA limit) for safe exposure in the mines. We promised to provide a report on the talc dust exposure of babies. We pointed out that the data we have is based on exaggerated dusting of a whole can of baby powder and that the amount generated, namely 345 mg/ m^3 may be excessive. We said that we are currently attempting to make the same calculation he proposed to the data. Our very preliminary calculation indicates that substantial asbestos can be allowed. safely in a baby powder.

Nuts

Hmmmm.

Dr. Wodicka appeared skeptical of Dr. Eiermann's approach to the problem. He implied that what is safe for a miner may not be safe for a baby.

Dr. Eiermann also mentioned that they were carrying out some studies in-house using an air sampler to assess the dust exposure and were having some difficulties in determining it.

Dr. Hildick-Smith reviewed the current knowledge on the biology of talc and indicated that talc had a low order of toxicity when evaluated in cell culture systems, that animal studies had been conducted which confirmed the cell culture studies, and that long-range inhalation studies in rats by MRC and in hamsters by J&J were being conducted in England and in the U.S.A. and that the results will be available in 1975. It was pointed out that two separate epidemiological studies had been conducted on talc miners, one by Dr. Kleinfeld and the other by Dr. Green at the University of Vermont School of Medicine in Burlington. The data obtained from both studies indicated that, where miners in the Kleinfeld study had been exposed to talc dust for an average of about 17 years and in the Green study for about 7 years, there appeared to be no significant impairment of the miners' health. Utilizing these data, the known information

concerning the amount of talc to which infants were exposed and their respiratory capacity, miners were exposed for a period of approximately 1,000 times that of an infant. The dose respired by the miner is approximately 11,000 times that respired by the infant. It was brought out that critical review of all the world literature failed to show any evidence of adverse health effects following the normal use of cosmetic talcs.

Dr. Hildick-Smith indicated that he was writing a review article on talc and that a copy of the manuscript would be sent to the FDA for their files.

Hmmmm!

Dr. Fuller stressed Johnson & Johnson's policy of full cooperation with FDA and that if the results of any scientific studies show any question of safety of talc, Johnson & Johnson will not hesitate to take it off the market.

A meeting was then held in Dr. Schmidt's office. The proceedings were similar to that which took place in Dr. Wodicka's office .

Dr. Schmidt asked for information on our Vermont mine: location (Windsor, Vt.), kind of talc (platey talc), processing (froth flotation to maximize platey talc). He wanted to know whether we sell our talc to other companies (cosmetic beneficiated grade is not sold to other companies; other locations in the Windsor mine are used to supply industrial grade talc).

Dr. Fuller pointed out that our meeting is not a "crisis" meeting. The Commissioner appeared to appreciate that. Dr. Fuller again stressed Johnson & Johnson's pplicy of full cooperation with the FDA which preceded the Kretchmer incident, namely, the Tenovus report where Dr. Hildick-Smith had called Dr. Simmons at the time we first heard of it. We reviewed briefly the Tenovus data (unreliable talc particle identification technique, presence of mineral particles in the tissue-fixing baths, lack of formal education of the principal investigator).

Dr. Hildick-Smith also commented briefly on the article relating stomach cancer in the Japanese and pointed out that this was generally discredited by scientists and that there was no information in the world literature or in animal studies completed to indicate talc produced cancer.

Dr. Schmidt said that the FDA could come under pressure from consumer or other groups and that they were particularly vulnerable when there were minimal, inadequate or no scientific data in a specific area. He had, however, developed a tactic by which he publishes in the Federal Register any scientific attack on the FDA in the hope that members of the scientific community could provide data to assist the FDA.

He appreciated the Johnson & Johnson visit and our expression of interest to assist the FDA where possible. He welcomed the opportunity of having a source of scientific information on which he could rely if the occasion arose. He indicated the immediate interest of the FDA in developing a method for assessing asbestos in talc. He pointed out that additional information being developed by Johnson & Johnson and others would meet the possible future need if talc per se is attacked. As there were some scientific data and good scientific studies in hand, the scientific community would be well prepared to withstand any on-slaught concerning talc.

The meeting ended on a very cordial note and appreciation by the FDA officials of Johnson & Johnson's visit and willingness to cooperate with the agency in developing methods and providing information concerning talc technology.

G. Hildick-Smith

W. Nashed

W. Nashed

cw

cc: Dr. R. A. Fuller
Dr. A. Goudie
Dr. G. Hildick-Smith
Mr. D. D. Johnston
Mr. G. Lee
Dr. D. Petterson
Mr. S. Smoyer
Dr. T. Shelley
Mr. H. Stolzer

Exhibit 103

Talc and Ovarian Cancer

Supplementary questions and answers
Prepared 20.10.97

Background
On 22nd October 1997, Face Value will air a programme, which will discuss a potential link between talc and ovarian cancer. This issue has been around for many years and there has been a full FDA review of all of the research available. This review has concluded that there is absolutely no causal link between talc and ovarian cancer. This is an industry matter and is not specific to Johnson's Baby powder. The CPTA has issued a full statement on the matter and Johnson & Johnson supports this statement.

The purpose of this document is to supplement the question and answer sheet already issued by J&J corporate . It covers issues specific to what may be aired during the Face Value programme . Any questions on the link to ovarian cancer or the similarities to asbestos are contained within the corporate Q&A also attached.

sponsored

Above all, the company is absolutely sure that Johnson's Baby Powder is perfectly safe for use on any part of the body, in line with the directions on the pack. There is no link to ovarian cancer either implied or actual and this is the conclusion of the independent review carried out by the FDA. Trust and safety is the basis of our company reputation and if we believed there was even the slightest risk associated with the normal use of Johnson's Baby Powder, we would not hesitate to take the necessary action.

Questions and answers in response to recent publicity. (numbered from Q.38 onwards which follows the corporate Q&A sheet)

Q.38: If you are saying that there is no link to ovarian cancer then why did the programme suggest that there is - they wouldn't just make it up would they?

A.38: That is a good question and we have challenged ourselves on the same issue. We are entirely confident of the safety of our product and all we can do to reassure you is tell you the facts : and that is that there is absolutely no link between talc and ovarian cancer. This is the view expressed by the independent FDA working party who have reviewed all of the research and is supported by the CPTA.

Q.39: Are you saying that the research is not valid in its conclusions?

A.39: What is most important here is what the independent working party who have reviewed this research have concluded. They have concluded that there is no link to ovarian cancer either implied or actual . We have also carried out our own review of the data and we support the conclusions drawn by the FDA.

Q.40: Why did Johnson & Johnson decline to be interviewed by Face Value?

A.40: The talc issue is a general industry issue and is not specific to Johnson's Baby Powder. The CPTA issued an industry response to Face Value , which we support . We are more than happy to talk to our consumers directly (as

Plaintiff's Exhibit No. P-115

exhibitsticker.com

I am doing with you now) but it is not our corporate policy to talk to our consumers through the medium of television programmes like Face Value.

Q.41: Why did the CPTA statement which J&J supports make no reference to the fact that the FDA went on to conclude that people should "err on the side of caution"?

A.41. The written FDA statements, which the CPTA have relied on to draw their conclusions, do not contain any such reference. If this is a personal or subsequent view verbalised by any member of the FDA then they are entitled to express that view. Ultimately we all have to take whatever action is right for ourselves. What I can assure you of however, is that Johnson's Baby Powder is perfectly safe for normal use and that the FDA formal conclusions were that there is absolutely no link either implied or actual to ovarian cancer.

Q.42: If you have known about this research since 1994 or before, why didn't you tell consumers before now or were you just worried about your sales?

A.42: We believe that our first responsibility is always to our consumers. This research has always been in the public domain and we have made no attempt to hide it. We have made every attempt to understand its implications for our consumers and can assure you that independent reviews of the research carried out by the FDA have concluded that there are is no link to ovarian cancer. Trust is the basis of our company reputation and I can assure you that if there was the slightest risk to our consumers we would be the first to withdraw the product. We have done this before with Tylenol in the US.

Q.43: If there is even the slightest risk of a link to ovarian cancer why do you say that the product is safe to use on babies, particularly on babies' bottoms?

A.43: We can assure you that there is not even the slightest risk of a link to ovarian cancer. Independent studies have proven that talc cannot migrate from any area of the body to the ovaries. Johnson's Baby Powder is perfectly safe to use on your baby, in line with the normal directions on the pack.

Q.44: Why would Face Value make a programme on this subject if there is nothing to it - surely I should believe them more than I should believe you because they have the consumers' interests at heart?

A.44: That is a great question and I cannot answer it for you. Our opinion is that it is the independent conclusions of the FDA working party that are the most reliable source of the truth in this matter. This working party concluded that there was absolutely no link between the use of talc and ovarian cancer. Ultimately you have to judge the accuracy of the information you have received from the media and from us. However, I can assure you that we always have our consumers' interests at heart and that if there was even the slightest risk we would act accordingly.

Q.45: I don't care if you think that there is absolutely no risk. You should have made consumers aware of the issue - there should be directions on the pack to indicate that it is not suitable for use on certain parts of the body. Are you going to do this in the future?

A.45: Ultimately, it is not what we think that matters, but what independent sources such as the FDA think. We are extremely confident in the FDA working party conclusion that there is absolutely no risk of ovarian cancer. Johnson's Baby Powder is safe for use, in line with the normal directions on pack, on any

part of the body. Research has proven that talc cannot migrate from any part of the body to the ovaries. We are extremely confident in the safety of our product and see no need to make any changes to the current packaging.

Q.46: I have just been diagnosed with ovarian cancer and I have been using Johnson's Baby Powder for years. I am extremely angry that you knew about this years ago and that you did not inform the public. I want to know how you are going to compensate me.

A.46: I am extremely sorry to hear about your recent diagnosis. However I can assure you that there is absolutely no link between Johnson's Baby powder and ovarian cancer. This is not just our view but is supported by an independent review of all of the research available conducted by the FDA.

If the consumer is still unhappy with this response and insistent upon what we are going to do to compensate her then the appropriate response is…

Once again, I am very sorry to hear that you are suffering from ovarian cancer, however I can assure you that our product is not at fault. If you wish to take this further then that course of action is up to you and we will respond accordingly.

Q.47: How can you be totally sure that talc does not cause ovarian cancer?

A.47: We are absolutely sure for a number of reasons: firstly, an independent review of all the research available , conducted by the FDA has concluded that there is no link between talc and ovarian cancer. Secondly, in the UK and the U.S where talc is commonly used, the incidence of ovarian cancer is 15 / 100,000 women whereas in Scandanavia where talc is not used by women the incidence of ovarian cancer is higher at 21 / 100,000 women. The higher incidence of ovarian cancer in Scandanavia is linked to diet and has no connection to the use of talc.. We can absolutely assure you that there is no known or implied link between talc and ovarian cancer. If there was we would be the first to take appropriate action for the safety of our consumers.

considered to be

□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□□
□-□□□Š□□□š□□□œ□□□Ý □□□
□□□
□□×
□□□
□□Y
□□&□□□'□□□T□□□□□□□B □□C
□□:!□□†!□□{$□□&P□□>P□□œP□□□ý□ù□÷□ò□ù□ù□ù□ù□ù□□ù□□□□□□□□□□□□□□□□□□□□□□□□□□
□□
□□
□□
□□
□□□□□□□□□□
5□□6□□>*□□H*□□5□□6□□□□5□□□□□□□□□□□□□□□□□D□□□E□□□n□□□^□□□‰□□□Š□□□•□□□"□□□"□□
□Õ□□□Ö□□□Û □□Ü □□Ý □□W
□□X
□□õ
□□ö
□□□
□□□
□□×
□□Ø
□□□
□□□
□□Y
□□ý□□□□□□□□□□□□ý□□□□□□□□□□□□ý□□□□□□□□□□□□ý□□□□□□□□□□□□ý□□□□□□□□□□□□ý□□□□□□□□□□□
ý□□□□□□□□□□□□ý□□□□□□□□□□□□û□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□
□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ê□□□□□□□□□□□□ó□□□□□□□□□□□□è□□□
□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□ó□□□□□
□□□□□□□ó□□□□□□□□□□□□ó□□□□□□□□□□□□□□□□□ □□□$□
„XûÆ□□□□%@□□□
„Xû□Æ□□□□%@□□□□□□□□□□□□□□□□□□□□□□□□D□□□E□□□n□□□^□□□‰□□□Š□□□•□□□"□□□"□□□Õ□□□Ö□□□Û
□□Ü □□Ý □□W
□□X
□□õ
□□ö

□□□
□□□
□□×
□□Ø
□□□
□□□
□□Y
□□Z
□□ó□□□ô□□□x□□□y□□□□□□□□□□□□&□□□'□□□□□□□,□□□#□□□$□□□S□□□T□□□□□□□-
□□□[□□□\□□□k□□□1□□□†□□□‡□□□†-□□‡-□□®□□¯□□B □□C
□□9!□□:!□□□□□□□□□□ü□ùöó□□ðíêåâßÜÙÖ□□□Ó□ÐËÈÅÂÀ½¸µ°-□ª§¤□¡œ™-
"À□□□À□□□□□çÿÿ□□'éÿÿ□□(éÿÿ□□□□□7êÿÿ□□□8êÿÿ□□vìÿÿ□□?íÿÿ□□@íÿÿ□□pîÿÿ□□□□□□ïÿÿ□□□□ï
ÿÿ□□□□□1ñÿÿ□□□mñÿÿ□□□□□□□òÿÿ□□□ôÿÿ□□□ôÿÿ□□□□□¿ôÿÿ□□□Àôÿÿ□□:öÿÿ□□¼÷ÿÿ□□□øÿÿ□□□øÿÿ
□□□ùÿÿ□□□ùÿÿ□□□□□;úÿÿ□□□<úÿÿ□□¶úÿÿ□□·úÿÿ□□¾üÿÿ□□ýÿÿÿ□□□þÿÿ□□□□□□□:Y
□□Z
□□ó□□□ô□□□x□□□y□□□□□□□□□□□□&□□□'□□□□□□□,□□□#□□□$□□□S□□□T□□□□□□□-
□□□[□□□\□□□k□□□1□□□†□□□‡□□□†-□□‡-□□®□□¯□□B
„XûÆ□□□□%@□□B □□C
□□9!□□:!□□…!□□†!□□z$□□{$□□÷□□□□□□□□□□□□□÷□□□□□□□□□□□□□÷□□□□□□□□□□□□□÷□□□□□□□□□□□□□÷□
„Xû
Æ□□□□%@□
:!□□…!□□†!□□z$□□{$□□□□□ü□□□
□□□□□□□□□□□□□□□□□□□□□□□□□□□□□àÿÿ□□□□°,. °ÆA!°□
"°□
#□ □$□ □%°□□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □
□w□r□i□t□t□e□n□s□t□a□t□e□o□p□e□n□a□v□a□i□l□a□b□l□e□,□S□c□a□n□d□i□n□a□v□i□a□h□i□g
□h□e□r□
□a□t□i□□

Exhibit 104

MEMORANDUM

TO: Sarah Colamarino, Owen Rankin, and John McKeegan

FROM: Kate Triggs

DATE: November 9, 2000

RE: Talc Issue

Further to our conference call on November 8th we have developed the following documents to aid discussion with senior management. Included in this is:

- A positioning brief for discussion with senior management
- A summary document for quick briefing
- A draft holding statement for use in the U.S.

In addition we have separated out the more detailed background briefing notes.

We will keep working on the scenarios and potential outcomes and implications of the NTP hearing and subsequent report and have recommendations on next steps. We will forward those to you by mid-week next week.

JOHNSON & JOHNSON CONSUMER

NTP – TALC

POSITIONING BRIEF

Background
A controversy surrounding talc has arisen in connection with a review by the National Toxicology Program (NTP), a program within the U.S. Department of Health and Human Services (HHS). The NTP has added talc to its list of Carcinogenic Agents, Substances or Mixtures in a preliminary draft of its Report on Carcinogens. The report itself is not conclusive. It is the first step in a lengthy review process designed to present a formal risk assessment, and does not result in regulatory action.

Proposed Position
J&J believes that the science shows talc to be safe. However, controversy surrounding the product in some markets may affect our customer's peace of mind. This in turn could impact the commercial viability of the product in that market.

Therefore, while we stand by the safety of talc, J&J in the US has made the decision to switch manufacturing entirely to cornstarch to ensure commercial viability of its powder products and to ensure customer peace of mind. This switch will take place by December 1st 2000

Special Considerations
By taking this position, J&J will disagree with a US government body that is claiming that talc may be a carcinogenic substance.

This position will require each market to make its own assessment of commercial viability and its own ingredient/manufacturing decision based on that.

JOHNSON & JOHNSON CONSUMER

NTP – TALC

SUMMARY BACKGROUND NOTES

Current status on Talc
The National Toxicology Program (NTP), a program within the Public Health Service (PHS) of the Department of Health and Human Services (DHHS), has added talc to the list of Carcinogenic Agents, Substances or Mixtures in the Report on Carcinogens. The NTP publishes the Report on Carcinogens as an informational scientific and public health document listing substances that may pose potential hazard to human health.

A draft Report is to be presented on December 13-14, to the NTP Board of Scientific Counselors' Report on Carcinogens (RoC) Subcommittee.

Carcinogens Report
What's critical to note is that while no regulatory action is taken as a result of this report, the media covers the hearings and the final publication of the report, with potential negative public reaction to a substance if it is listed in the Report. The Report does not present risk assessments nor does it establish risk or benefit – NTP acknowledges that is the responsibility of regulatory and research agencies.

Media
Media will be in attendance at the hearing. However, the majority of media will be trade journals covering the specific substance under review. We should expect light coverage in the trades following the hearing. According to past coverage of hearings, mainstream, national media will not cover the hearing. The majority of the national coverage is published the official Report is issued – in May or June following the Subcommittee hearing.

The Hearing
The Subcommittee meeting is a 2-day event, and is open to the public, including media. The agenda covers the peer review of agents, substances, mixtures, or exposure circumstances nominated for listing in the 10th *Report on Carcinogens,* and includes an opportunity for public input. A majority vote is then taken by the Subcommittee members to list or de-list the substance.

Public notice of the meeting was given and those requesting time to make public comments can request a time with the NTP's executive secretary by December 1, 2000. Following the meeting, an additional 60 days is allowed for public comment.

Report Impact
News from the report is covered widely in trade and mainstream media. In addition to potential impact on product sales, the Report prompts listing under the California Safe Drinking Water and Toxic Enforcement Act of 1986, requiring a warning label in that state and inclusion of the information on Material Safety Data Sheets under OSHA, which has a knock on effect nationwide.

NTP Review Process
The NTP has a seven-step review process for examining substances:

- Nomination of substance for review
- National Institute of Environmental Health Sciences Review Group
- Interagency Working Group
- NTP Board of Scientific Counselors, Report on Carcinogens Subcommittee ***(Currently where talc is in the process)***
- Review by the NTP Executive Committee and NTP Director
- Final review by Secretary, Health and Human Services

JOHNSON & JOHNSON CONSUMER

NTP – TALC

DRAFT HOLDING STATEMENT

Johnson & Johnson intends to discontinue its use of talc in all of its consumer products in the U.S. Beginning December 1, 2000, the company's U.S. manufacturing operations will switch to cornstarch.

The following is a general statement describing Johnson & Johnson's position on this issue:

"At Johnson & Johnson consumer safety and satisfaction is our bottom line. We have worked tirelessly to ensure that J&J products meet the highest standards of safety and satisfaction – all of them, including the talc products we intend to change.

"We stand by the safety of our talc products. Our commitment to the safety of talc is based on the extensive scientific research conducted in over a century of manufacturing of talc products. These J&J products are completely safe and always have been.

"However, we want our customers in the U.S. to have peace of mind. They should never harbor even the slightest doubt about the safety of our products. So, rather than debate the merits of our popular, time-tested talc products, we will switch operations to cornstarch instead."

Exhibit 105

Your questions deserve answers.

The talc in Johnson's Baby Powder is the purest, safest pharmaceutical-grade talc on earth. It doesn't contain asbestos and never will. We test every single lot to ensure it.

The FDA has tested Johnson's talc since the '70s and has confirmed - every single time - that it did not contain asbestos.

We have always cooperated fully and openly with the FDA and other regulators and have given them full access to our talc testing results.

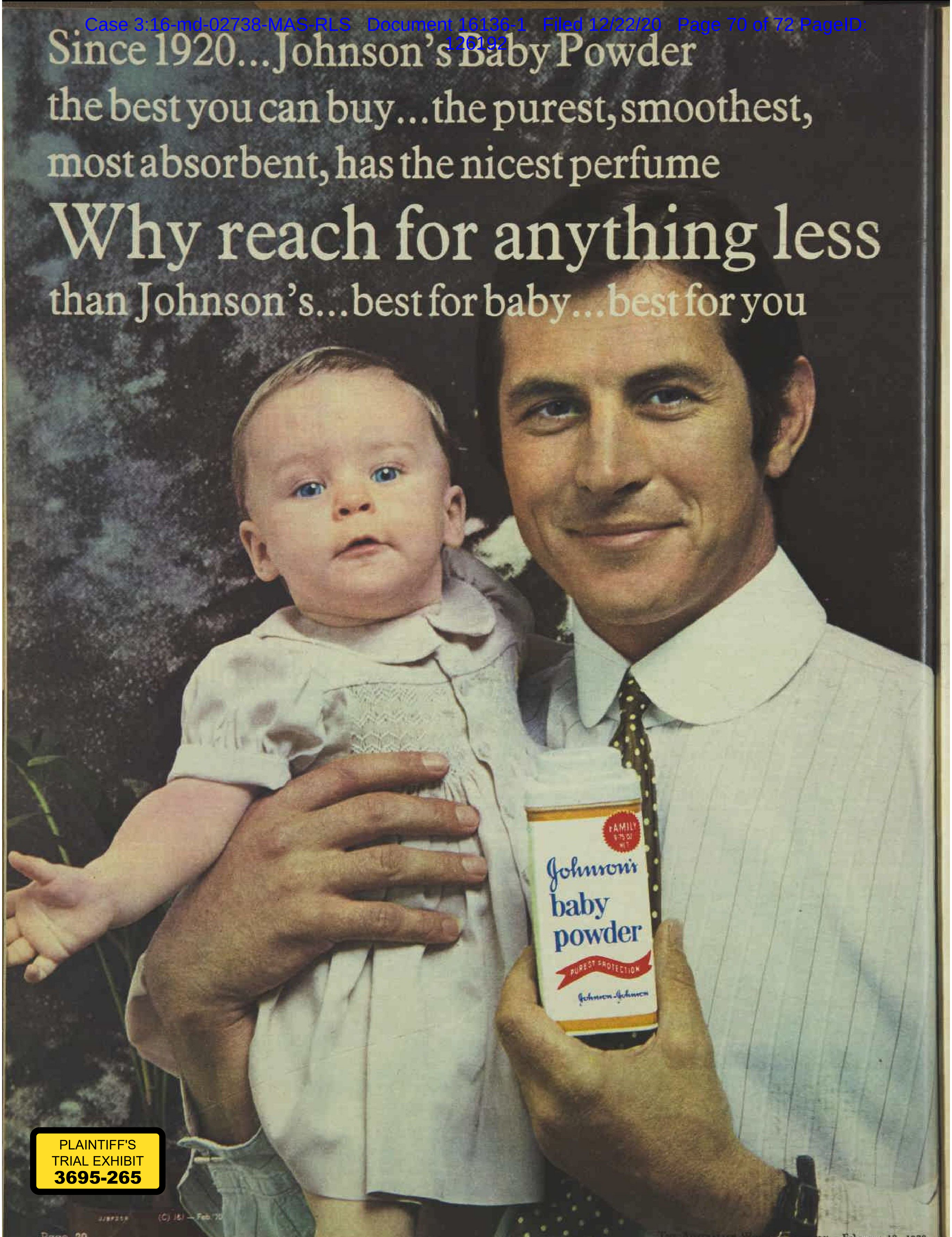
We did not hide anything. Ever. Our openness and collaboration with the FDA and regulatory agencies is well documented.

We have always acted with the utmost transparency in this matter. Nothing is more important to us than the health and safety of our customers. We're parents and grandparents, just like you. If we had any reason to believe our talc was unsafe, it would be off our shelves immediately.

There is irrefutable scientific evidence that our talc is safe and beneficial to use. Go to factsabouttalc.com. There you'll find independent studies from leading universities, research from medical journals, and third-party opinions, so you can learn the facts and make up your own mind.

Johnson & Johnson

Exhibit 106



PLAINTIFF'S
TRIAL EXHIBIT
3695-265

Let our family take loving care of yours.

Remember when your mother took care of you with JOHNSON's baby products? How good it made you feel? Well, you can feel that way again. You, and those you love.

Everyone, including the man of the house, will enjoy the fresh, clean feeling of pure JOHNSON's Baby Powder.

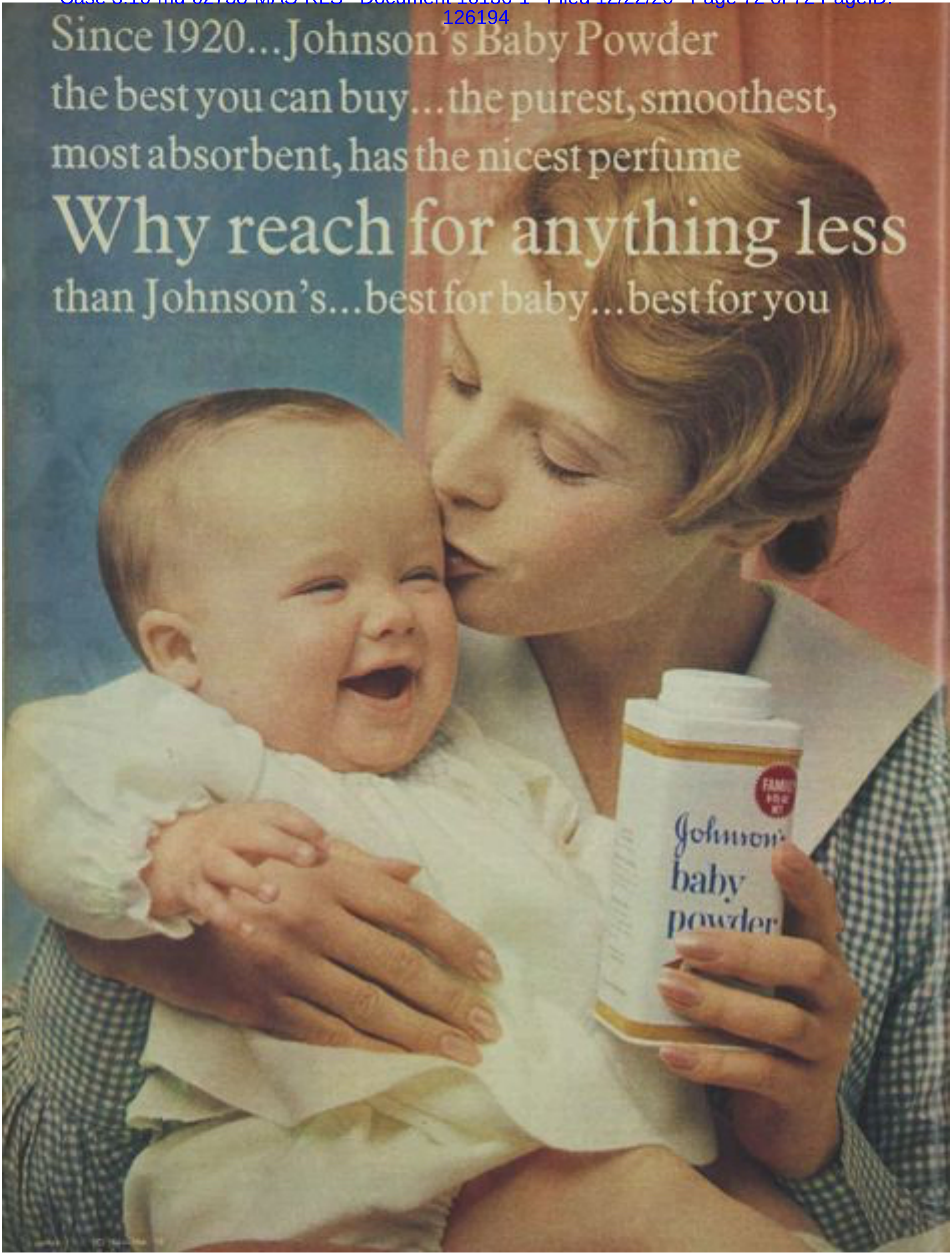
And thick, rich JOHNSON's Baby Lotion will help keep the whole family feeling soft and smooth. So they won't have to worry about the kind of dryness that shows.

JOHNSON's Baby Shampoo cares for your entire family with a trusted "No More Tears"™ formula that cleans hair gently, leaving it healthy-looking with a natural sheen.

JOHNSON's Baby Oil not only helps take care of your baby in lots of ways. It also works in many ways as a beauty oil for you.

Our JOHNSON's baby products have helped take care of families for almost fifty years. And we can help take loving care of yours.

Johnson & Johnson


Since 1920...Johnson's Baby Powder
the best you can buy...the purest, smoothest,
most absorbent, has the nicest perfume
Why reach for anything less
than Johnson's...best for baby...best for you
Johnson's
baby
powder